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THE ANTITOXIN UNIT IN DIPHTHERIA.

THEOBALD SMITH, M.D.

The action of antitoxin upon toxin appears more and more in the light of a true chemical reaction. That is to say, these bodies combine with one another and their individuality is thereby destroyed. This combination is governed by definite quantitative laws. Unfortunately the only at present available method of studying these laws is to determine, upon susceptible animals, the effect of mixtures of the two substances — a method exceedingly tedious and expensive.

The original method of testing the strength of antitoxins, or their toxin-destroying power, consisted in mixing ten times the minimum fatal dose of any toxin, towards a 250-gram guinea-pig, with different quantities of antitoxic serum, and injecting the mixture into the subcutis. That quantity of serum which completely neutralized the pathogenic action of this amount of toxin contained $\frac{1}{10}$ antitoxic unit. This unit, which like all other units is an arbitrary standard, may be contained in one cubic centimetre of serum or in $\frac{1}{100}$ cc. or even in $\frac{1}{1000}$ cc. In any case $\frac{1}{10}$ of this quantity was sup-

posed to destroy 10 m. f.¹ doses of toxin. The method of mixing toxin and antitoxin before injection into guinea-pigs instead of injecting them separately was introduced by Ehrlich and it has replaced all other methods. The antitoxic unit of Behring-Ehrlich has also displaced other methods of expressing antitoxic power on account of its simplicity.

The presumption involved in this method of testing antitoxin was that 10 times the m. f. dose of any diphtheria toxin is a uniform factor which could be obtained by any one by determining the m. f. dose of any toxin to be used as a measure. But in 1896 Ehrlich, then made director of the new Prussian Institute for the study of toxins and antitoxins, found that the same antitoxin neutralizes a variable number of fatal doses of toxin according to the culture used and perhaps the method of preparing the toxin. The original antitoxic unit was supposed to neutralize 100 m. f. doses of toxin, whereas it was found that the same amount of the same antitoxin might neutralize from 30 or less to 130 doses, according to the source of the toxin. It became, therefore, necessary to establish a new method of standardizing diphtheria antitoxin. Ehrlich accomplished this by preparing dried toxins and antitoxins, and preserving them as powders in vacuum tubes protected from the light and kept at a low temperature. These tubes are opened from time to time and the contents used in preparing standard dilutions. The standard dilution of antitoxin is made by Ehrlich in equal parts of glycerine and 10 per cent. salt solution, a menstruum which maintains the strength of the antitoxin dissolved in it constant for several months.

It was at one time supposed by Ehrlich that the more profound study of toxin-antitoxin mixtures might yield some general formula capable of restoring the unit when lost, but recent investigations indicate such complex relationships that a theoretical unit cannot be looked for in the near future.

The facts I have stated are illustrated in the work of

¹ These abbreviations, indicating "minimum fatal," will be used throughout this article.

Ehrlich and Madsen¹ and what is here recorded is simply a repetition of Ehrlich's work. I clearly perceived some years ago that it would be useless to continue to use the old method of testing antitoxins and therefore gave it up for the newer one. For more than three years I have been supplied every two or three months with standardized antitoxin from the Institute, now permanently located at Frankfort, of which Professor Ehrlich is the director. With this test serum all the antitoxin prepared for the Massachusetts State Board of Health has been tested and all the figures I shall give have been obtained. In establishing a more rigid standard Ehrlich at the same time made certain important modifications in the method of testing which increase its accuracy. He used the entire unit instead of only one-tenth unit in the operation of standardizing and, in place of making complete neutralization the end to be obtained, he shifted the end reaction to the death or survival of the guinea-pig used. For example, if we have in hand the unit antitoxin and desire to standardize a certain toxin we add to the antitoxin such excess of toxin that the resulting mixture will just prove fatal to a guinea-pig on the 4th day. Theoretically this means that we have added not only enough toxin to neutralize the antitoxin but also one additional minimum fatal dose. This point Ehrlich denominates L_+ . The amount of toxin needed to neutralize completely the antitoxin he denominates L_0 .

Let us now see from actual figures how the same antitoxic unit may neutralize different amounts of toxin. My results obtained since 1898 are best seen in tabular form. It should be borne in mind that the figures given in Table I. are simply selections from a considerable number made from time to time.

¹ Ehrlich. *Ü. d. Constitution des Diphtheriegiftes*. Deutsche med. Wochenschr., 1898, no. 38; *klinisches Jahrbuch*, 1897, vi.

Madsen. *La Constitution du Poison diphtérique*. Annales de l'Inst. Pasteur, 1899, p. 568.

Ehrlich. *Jenner Institute of Preventive Medicine*, 1899.

TABLE I.
Standardization of Test Toxins.

TEST TOXIN.		Number of bacillus used.	Date of test.	Minimum fatal dose.	L ₀ dose.	L+ dose.	L+ — L ₀ in m. f. doses.
No.	Date of preparation, and days in incubator.						
7	June, 1898 (9 days)	14	Oct., 1898	0.035 cc.	1.5 cc.	1.88 cc.	53.7 — 42.8 = 10.9
8	Oct., 1898 (10 days)	14	Sept., 1899	0.0074	0.32	0.425	57.4 — 43.2 = 14.2
9	Oct., 1898 (8 days)	47 (= No. 8 of Park and Williams)	June, 1899	0.0023	0.145	0.185	(a) 80.4 — 63 = 17.4
			Aug., 1899	0.0025	0.145	0.186	(b) 74.4 — 58 = 16.4
			Oct. 3, 1900	0.0033	0.16	0.205	(c) 62.1 — 48.4 = 13.7
10	Nov., 1899 (7 days)	47	July, 1900	0.0042	0.17	0.23	54.8 — 40.5 = 14.3

In this table the column marked L₀ represents the amount of toxin (culture filtrate) which is completely neutralized by one antitoxic unit. The column marked L+ indicates the amount of toxin which must be added to one antitoxic unit in order that the mixture may just prove fatal to a guinea-pig of about 250 grams. An examination of the last column shows us that the unit antitoxin neutralizes from 40 to 63 m. f. doses according to the toxin employed. In other words, a serum standardized according to the old method with toxin No. 10 as a 200-unit serum would actually be $2\frac{1}{2}$ ($\frac{100}{40}$) times as strong as one marked 200 units with the same test toxin according to the present Behring-Ehrlich unit. Again a serum standardized with toxin No. 9a, as 100 units strong, would be only $\frac{40}{63}$ as strong as one found by the same method to contain 100 units with toxin No. 10.

It might be claimed, as has been done by Park and Atkinson,¹ that if toxins are prepared in absolutely uniform manner from the same culture, the neutralizing power is likely to be the same. This may and may not follow. Toxins No. 7 and 8 of Table I. were prepared in the same way from the same

¹ Journal of Exper. Medicine, 1898, iii, p. 513.

culture and although the toxicity of No. 8, owing to certain procedures¹ employed in preparing the culture medium, is nearly five times as great as that of No. 9, yet the L_0 dose is nearly the same (42.8 and 43.2 m. f. doses). On the other hand, though toxins 9 and 10 have been prepared in the same way, the L_0 dose in 9a is 63 and in 10, 40.5 m. f. doses. We cannot, therefore, be certain that the combining power of different toxins from the same culture will be the same.

It should also be noted that in the 4 test toxins on Table I. the m. f. doses neutralized completely (L_0) or to the L_+ limit fall far below 100, the limit of the old method. Such toxins used in the old way would greatly undervalue the sera standardized with them, as I have already pointed out.

The gap between the old and the new method is well brought out by testing the toxins according to the former with one-tenth of a unit (Ehrlich).

Assuming according to the original method that $\frac{1}{10}$ anti-toxic unit should completely neutralize 10 m. f. doses, we have the following result with toxin No. 8:

10 m. f. d. + $\frac{1}{10}$ unit = death in $1\frac{1}{2}$ days.
 7 m. f. d. + $\frac{1}{10}$ " = death in $7\frac{1}{2}$ days.
 5 m. f. d. + $\frac{1}{10}$ " = slight transient oedema.

Here instead of neutralizing 10 doses it fails to neutralize 7 and even with 5 doses there is a trifling excess of toxin. This result agrees precisely with the tabulated L_0 dose of the entire unit, which is 43.2. In this way the inadequacy of the old method was demonstrated with toxin No. 9.

Aug. 5, 1898. 58 m. f. d. + 1 unit = complete neutralization (L_0).
 10 " " + $\frac{1}{10}$ unit = death in $2\frac{1}{2}$ days.
 8 " " + " " = large slough.
 6 " " + " " = transient oedema.

Here also the L_0 dose — 58 m. f. doses — agrees with the $\frac{1}{10}$ unit test which demands for complete neutralization a trifle less than 6 m. f. doses. With toxin No. 8, under the old system, serum would be standardized 100 instead of 200 units; with No. 9, 100 instead of 166 units.

¹Theobald Smith. Journal of Exper. Medicine, 1899, iv, p. 373.

Why the combining value of these toxins should be uniformly low I am unable to state. It is possible that the method of preparing the bouillon which I described in a former publication¹ may account for it. This method, which furnishes a concentrated toxin, may at the same time lead to other modifications of the toxin, in virtue of which its various components are present in proportions different from those obtained by older processes.

The table furthermore shows that when the same toxin is kept under suitable conditions the results are remarkably uniform from month to month and only very slight changes in dosage are required to meet the slow deterioration of the toxin. The standardized toxins referred to in the table were kept in drachm vials, which were filled, tightly corked, and kept in the dark in a tight wooden box in a cellar under lock and key. One vial was opened for each test and the unused portion rejected. In Table I. the last test of toxin No. 9, fully two years after its preparation, shows considerable loss of toxicity and only a slight loss of combining power. This toxin was no longer in use and the test is here introduced simply to illustrate the very slow change in the L_+ dose. The difference between (*a*) and (*c*) is only 10 per cent., which would not have been a serious one even if the toxin had not been restandardized for a whole year. As a matter of fact, the test toxin is reëxamined every month or two. It is probable that better results would have been obtained by adopting Ehrlich's method of keeping the toxin under a layer of toluol.

The results obtained with the use of Ehrlich's standard serum are on the whole so remarkably satisfactory and the method so delicate that the one making the tests soon insists on having the most accurately calibrated pipettes, as recommended by Ehrlich, capacity pipettes for thicker fluids like the standard antitoxin and serums, and outflow pipettes for the dilutions.

One of the variable factors to be reckoned with are the guinea-pigs. Even when animals of only certain weights are

¹ *Loc. cit.*

used, — and only those between 250 and 280 grams come into consideration, — animals are occasionally found which are able to stand a single fatal dose without any local reaction whatever. These are very rare. I have encountered four which were immune to this dose (out of 600 to 700) during the past two years, all from the same mother in two litters. When animals are reared together they react very uniformly. Those brought from other places must first be carefully tested. I have found certain purchased lots fully twice as susceptible to toxin as my own. There is also a somewhat vague curve of resistance among animals of the same breeding from winter to summer. Guinea-pigs are to all appearances more susceptible in winter than in summer. This fluctuation appears in the determination of the m. f. dose and the L_+ dose, but I am unable to give it at present any quantitative expression.

It is not my purpose to go into any discussion of the many theoretical questions raised by Ehrlich in his studies of toxin-antitoxin mixtures. This has been in part done by Park and Atkinson,¹ but since that date the continued researches of Ehrlich and Madsen have indicated so great a complexity of the neutralization phenomena that any hypothesis fails to explain them. Ehrlich has shown, among other things, that if we add to a definite quantity of toxin different fractions of the antitoxic unit, — if we, in other words, saturate this amount of toxin in different degrees, — we obtain results which indicate that the neutralizing and the toxic power of the same toxin do not go hand in hand. If we, for example, add to the L_0 dose of toxin half an antitoxic unit we may find, according to the toxin used, that not necessarily half of the toxic doses have been neutralized, as the calculation would imply, but perhaps 25% or 75%. Ehrlich has, by a study of various toxins, inferred from these results the existence of substances of different degrees of toxicity, as well as neutralizing power towards antitoxins, which in virtue of the numerous combinations in which they may appear in our toxins lead to a multiplicity of variations.

¹ *Loc. cit.*

The substances which appear in the fresh toxins are classed by him as toxins and toxones. The latter have little or no toxicity, but they neutralize antitoxin, and he regards them as the feeble poisons which produce paralysis. According to their affinity for antitoxin, he classifies the toxins occurring in any culture fluid into proto-, deuterio-, and tritotoxins. The proto-toxins have the strongest, the toxones the least, affinity for antitoxin. These break up after a time into toxoids (proto-, deuterio-, and tritotoxoids). Some of these secondary products are more stable than others.

By constructing graphically the results obtained by saturating the same L_+ or L_0 dose of toxin with different fractions of the antitoxic unit, Ehrlich has obtained what he calls toxin spectra, in which the relative affinities of these hypothetical components of the toxic fluid are mapped out. Similar spectra have been published by Madsen. From an analysis of these varied spectrum phenomena Ehrlich concludes that in the toxin molecule "there are two mutually independent atomic groups. One of them is of haptophorous character and effects the union to the antitoxin, or to the lateral chains of the cells corresponding to it. The other atomic group is toxophorous, *i.e.*, it is the cause of the specifically toxic action." The haptophorous group is relatively stable, while the toxophorous group is unstable, fermentlike. Hence the relative constancy of the combining power with the continuous reduction of toxicity.

The low combining power of my toxins induced me to study the "spectrum" of one of them more closely. Owing to various interferences the test extended over the period of a whole year, during which time the toxicity of the fluid used underwent some deterioration, which is, however, accounted for in the table given below. The method consisted in adding to the L_+ dose different fractions of the antitoxic unit and determining the number of fatal doses left unneutralized.¹ The L_+ dose chosen at the outset was a trifle high, but it was maintained throughout.

¹ The method of determining the excess in m. f. doses consists in making dilutions of toxin and antitoxin, mixing them in the proper proportion demanded by the in-

TABLE II.
Toxin No. 8.

Date of test.	Min. fatal dose, cc.	L ₀ dose, cc.	L + dose, cc.	Fractional satu- ration.	Actual toxic doses in ex- cess.	Calcu- lated ex- cess in toxic doses.
Sept. 7, 1899..	.0075	.32	.425	Unit Toxin. Antitoxin.		
Oct. 12, 18993243 cc. + $\frac{170}{200}$	4-5	10
Nov. 22, 1899.425	.43 cc. + $\frac{180}{200}$	6	
Dec. 2, 1899..43 cc. + $\frac{150}{200}$	8	
Dec. 15, 1899.43 cc. + $\frac{180}{200}$	12	
Dec. 22, 1899.425	.43 cc. + $\frac{100}{200}$	20	29
Jan. 1, 190042	.43 cc. + $\frac{80}{200}$	22	
Jan. 9, 190043 cc. + $\frac{80}{200}$	24-25	
Jan. 18, 1900.43 cc. + $\frac{60}{200}$	29	
Mar. 9, 1900..43 cc. + $\frac{50}{200}$	32	42
Mar. 14, 1900. .007842	.43 cc. + $\frac{40}{200}$	33-34	
May 5, 1900..43 cc. + $\frac{80}{200}$	37	
June 23, 1900.43 cc. + $\frac{25}{200}$	38	
Sept. 19, 1900.43 cc. + $\frac{15}{200}$	less than 42	
Sept. 28, 1900. .0134+	.425	.43 cc. + $\frac{10}{200}$	39	40

The table illustrates that for this toxin the saturation phenomena are fairly uniform in character. The number of fatal doses left unsaturated lag considerably behind the calculated number (assuming the toxicity to be uniform throughout), indicating the presence of tritoxoids of low toxic power and some toxones. The progress from beginning to end is fairly uniform, and the slight irregularities are largely due to

dividual test, and injecting into a guinea-pig that fraction of the mixture whose denominator represents the number of suspected m. f. doses in excess. If, for example, we anticipate the m. f. doses in excess to be near 40, we would inject $\frac{1}{38}$, $\frac{1}{40}$, $\frac{1}{42}$, etc., into guinea-pigs.

the fact that with this toxin the m. f. dose was not sharply definable.

The results suffer in accuracy on account of the long period of time over which the test has extended. It will be noticed that the m. f. dose rose rapidly during the latter period of the test, thereby making the calculated number of fatal doses smaller at the end than in the course of the experiment. The constancy of the L_+ dose, in spite of the shifting of the value of the m. f. dose, is well brought out and speaks in favor of the method of Ehrlich, which uses this limit for the practical testing of diphtheria antitoxins.

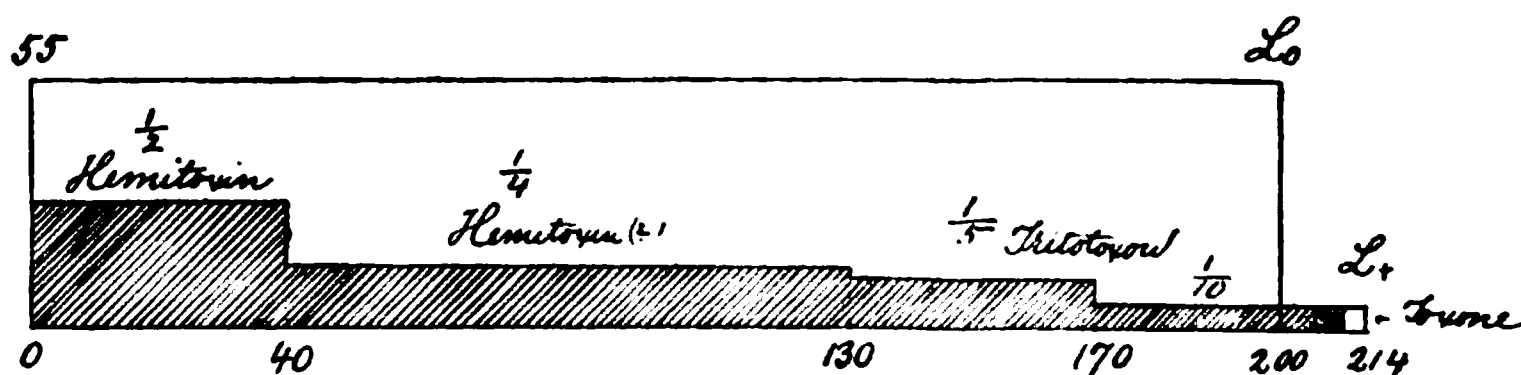


FIG. 1.

In Figure 1 I have attempted to represent graphically the results given in Table II. The construction of the spectrum is attempted on the basis of that part of the work which was done before the marked fall in the toxicity of the toxin used. The number of combining elements or units in the single antitoxic unit is assumed with Ehrlich to be 200, the number of actually toxic units (m. f. doses) being but 43. The partial saturation shows that in the right hand portion of the spectrum there is some hemitoxin, 40 combining units neutralizing 20 doses. In the next portion there are about twenty-two doses for 90 combining elements and the toxicity continues to decrease to the L_+ dose. It shows throughout the absence of any pure toxin, the nearest approach to it being the hemitoxin at the beginning of the spectrum. For illustrations of other rather remarkable types of spectra the reader is referred to Ehrlich and Madsen's papers.

The facts which have been presented in the foregoing pages, and which are the summary of a large amount of de-

tailed work, entitle us to agree with Ehrlich that the old method of using 10 times the m. f. dose as a standard for testing the antitoxic strength of sera is not reliable, even when the toxins are prepared under uniform conditions, and that at present we can do no better than utilize the standard provided by him.

THE SERUM REACTION IN FŒTAL AND INFANTILE
TYPHOID.

JOHN LOVETT MORSE, A.M., M.D.

(*Abstract.*)

The serum reaction occurs in infantile as in adult typhoid.

There are no data as to whether or not it occurs in fœtal typhoid.

The agglutinating power may or may not be present in the blood of infants born of women with typhoid. If present, it is transmitted from the mother to the child through the placenta. It is possible, however, that it may be formed in the child in response to toxines transmitted through the placenta. The agglutinating principle can pass through the normal placenta. Part of it, however, is arrested in the passage. Whether or not it is transmitted seems to depend on the strength of the agglutinating power in the maternal blood, and the length of time during which the placenta is exposed to it.

It may be transmitted to the nursling through the milk. It may appear in the infant's blood in less than twenty-four hours. It lasts but a few days after the cessation of nursing. It is always weaker in the milk than in the maternal blood, and always weaker in the infant's blood than in the milk. This weakening of the agglutinating power is due to obstruction to its passage in the mammary gland and in the nursling's digestive tract. The chief factor governing transmission is the intensity of the power in the maternal blood. A subordinate but important factor is some unknown condition in the digestive tract. If the power in the maternal blood is weak and the obstacles great it may not be transmitted.

ARTIFICIALLY PRODUCED MITOTIC DIVISION IN
UNFERTILIZED ARBACIA EGGS.

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What causes cells to divide is a question of importance in many different fields of biology. Cell multiplication is the fundamental fact of embryology, as it is of many pathological and physiological processes. Our actual knowledge of the determining causes of the process is fragmentary, and, as far as experimental knowledge goes, of very recent origin. It has long been known that the egg cell is awakened to division by the entrance of the sperm, and that many bacteria cause both animal and plant tissue cells to divide. Among such bacteria the tubercle bacillus is preëminent and it is a matter of some interest that according to Ruppel (1) the chemical constitution of the tubercle bacillus resembles that of the spermatozoa. In plants the well-known gall formations following the sting or deposition of the eggs of certain insects constitute a marked response by cellular division on the part of the plant tissues to a definite stimulus. In some galls the mechanical injury to certain cells by the jaws of the insects results in multiplication of other cells in the neighborhood of the injury. In other cases it is only when the larva has become free and begun to destroy the surrounding cells that the gall begins to form. These facts clearly pointed in the direction of certain chemical substances as effective causes of cellular division. The observations of Buchner that division of leucocytes and fixed connective-tissue cells follows injection of extracts of peas, beans, and the bodies of many bacteria may be interpreted in the same sense. There have long existed, too, observations on the stimulating effects of developing embryos on surrounding tissue cells which are hardly capable of any other interpretation. I refer to the multiplication of the follicle cells about the egg of Salpa after fertilization of the egg. In this case the embryo is for a time composed very largely of follicle cells instead of egg

cells. In plants there is the usual development of the cells of the embryo sac after fertilization of the ovule.

Plain though the indications of chemical fertilization have been for many years, the first fruitful experiments in this direction were those of Morgan (2) in 1898. Hertwig (3) had, it is true, observed some three years earlier that strychnine sulphate would cause an abnormal segmentation accompanied by karyokinesis in the sea-urchin egg, but this observation remained isolated. Morgan found that unfertilized star-fish, sea-urchin, and other eggs placed for an hour or more in sea water, to which had been added two per cent. or more of NaCl, MgCl₂, or KCl, would, on returning to normal sea water, segment irregularly into several cells, sometimes numbering as high as sixty. Morgan was interested chiefly in the cytological phenomena and failed to perceive the fundamental importance of his discovery. About the same time Mead (4) found that in certain solutions of KCl the eggs of *Chætopterus* could be made to develop the karyokinetic figures. In 1899 Morgan (5) confirmed the action of strychnine sulphate and suggested that the egg would respond to certain stimuli by division just as the muscle cells respond by contraction. In reality, however, the egg resembles more nearly the nerve cell, as we shall shortly see. Loeb (6) in 1899 confirmed Morgan's work and succeeded by properly regulating his salt solutions in carrying the embryo to full development. Loeb's first view was that the division was the result of the replacement of certain calcium or sodium ions in the egg by magnesium. This view was, however, plainly incorrect and he has in the past year modified it (7), so that we now know that the result is brought about by the increase in osmotic pressure of the sea water, thus causing water to leave the egg. Division may be produced by sugar or other solutions of non-electrolytes of sufficient strength. We thus have, finally, the first definite result—that cell division may be set up by any means which causes the cell to lose water, and by strychnine.

Loeb also found that a very short immersion of sea-urchin eggs in sea water either slightly acid or very slightly alkaline

would start division. The second point was thus made that a change in alkalinity would induce cell division.

During the past summer Loeb (8) has found, too, that in the annelid *Chætopterus*, but not in any other form so far observed, the substitution by potassium for other salts in the sea water would cause division with no change in osmotic pressure. Potassium in certain cases becomes hence a stimulus to division, and this may perhaps be connected with the physiological action of the drug.

My own experiments were carried on coincident with but independent of Professor Loeb's, and have resulted in extending our knowledge of the means by which cells may be made to divide. I have succeeded in setting up cell division in unfertilized sea-urchin (*Arbacia*) eggs by depriving the eggs of oxygen, by the action of heat, by subjecting them to the action of ether, alcohol, and chloroform.

Lack of Oxygen.

The eggs were placed in sea water in Engelmann gas chambers, and well-washed hydrogen gas led through for fifteen minutes to expel the oxygen. The eggs were then exposed to the air for ten minutes, and the hydrogen again let in for fifteen minutes to half an hour. On returning the eggs to fresh sea water, cell division, accompanied by karyokinesis, begins, and the majority of the eggs divide in the course of one to three hours into two or several cells. The nuclear figures are small as a rule. A multipolar spindle is formed, and the division is irregular.

Heat.

If the eggs be heated to 31° – 32° C. for two to four minutes, on returning to cool sea water the same phenomena ensue as in the gas chamber.

Alcohol, Chloroform, and Ether.

Exposure of the eggs to sea water saturated with ether for ten to fifteen minutes and then returning them to sea water causes division. The same result is accomplished by chloro-

formed sea water, with the exception that more eggs are killed. Alcohol added in the proportion of 1 c.c. 50% alcohol to 10 c.c. of sea water has a similar intoxicating effect.

Conclusions.

The foregoing results are of main interest because they may throw some light on the nature of the division process itself. All the methods thus far found for inducing cells to divide are the methods in common use for causing protoplasm to liquefy. Protoplasm is in a semi-solid state and passes with the greatest ease into a liquid state. This change is always going on in parts of the cell. The change may be seen most strikingly in mucous cells when the fairly solid protoplasm is converted into semi-fluid mucin. In fact, the maintenance of the semi-solid state of protoplasm is closely dependent on the respiration of protoplasm, as was long ago pointed out by Hoppe-Seyler (9). Protoplasm contains a large number of anhydrous substances which are broken up or saponified with great ease. We can in fact cause complete liquefaction of protoplasm by depriving it of oxygen, by submitting it to the action of OH or H ions, by taking water from it, by slightly increasing its temperature, by submitting it to the action of certain poisons, such as strychnine, alcohol, ether, chloroform, and so on. These methods, then, are all of them methods for producing liquefaction in protoplasm, and they strongly indicate that the old view of Bütschli (10) — that the karyokinetic figure itself is but the expression of the movement of liquid in the cell — is true. We come hence to the conclusion that any means which will produce localized liquefaction in the egg cell will set up karyokinesis.

This result is in direct opposition to a view suggested by me (11) last year that possibly the karyokinetic figure represented a clotting of the cell. That view I now believe to have been erroneous and that Loeb's suggestion that we are dealing with a liquefaction is correct.

The question naturally arises here whether these several agencies set up liquefaction by direct action themselves, or whether they interfere in some way with the respiration of

the cell, leading thereby to the production of a liquefying enzyme, the centrosome. The general phenomena of division strongly suggest a digestion of certain cellular structures, the nuclear wall, nucleolus, yolk, and certain chromatin constituents. In this connection it may be mentioned that Hahn and Geret (12) have recently shown, also, that any means which interfere with the life of the yeast cell lead to the production in it of a digestive ferment called endotrypsin. This may possibly be a closely analogous case. Farther investigation is necessary to settle this point.

In closing I wish to emphasize the analogy between the egg and nerve cell. The means which cause cell division or liquefaction are strong stimulants to the nerve cells, for example asphyxia, strychnine, and chloroform. This indicates that in the production of a nerve impulse we are dealing also with a liquefaction of some portion of the cell body.

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THE TOXIC EFFECTS OF FORMALDEHYDE AND FORMALIN.

(A PRELIMINARY COMMUNICATION.)

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Three guinea-pigs, four rats, a dog, and a cat were subjected for varying lengths of time to the inhalation of formaldehyde, generated by volatilizing paraformaldehyde pastils in a Schering disinfecting lamp, in a room of 5.5 cu. m. capacity. The animals developed a pneumonia, bronchitis, and tracheitis which varied in intensity according to the concentration of the gas and the length of the exposure. A beginning pneumonia was found in animals exposed in the room for one and one-half hours, during which time only 3 gms. of paraformaldehyde were volatilized. The pneumonia is primarily eosinophile; the eosinophiles are followed by the other polynuclear leucocytes, and these in turn by large and small mononuclears. The leucocytes are found in the alveolar walls, and in isolated patches filling one or more alveoli. There are accompanying changes in the cells of the parenchyma, vascular congestion and exudation. The bronchi are filled with serum, leucocytes, desquamated and degenerated bronchial epithelium, cellular debris, and mucus. The tracheitis is characterized primarily by eosinophile leucocytic infiltration; this is followed by infiltration with the other forms of polynuclear leucocytes and accompanied by vascular congestion and degenerative changes in the bronchial epithelium. Cultures from the lungs, bronchi, and trachea were nearly all negative, so that it is believed that the pneumonia is due to the inhalation of the noxious agent, and not to a secondary infection with bacteria.

Eleven animals — rabbits, kittens, and a dog — received injections into the stomach of varying amounts of formalin of strengths varying from 1 per cent. to the concentrated chemical. Sudden death resulted in three animals; one lived an hour, another forty hours; two were killed after a month; the remainder died at varying intervals in from three

to nine days. The symptoms following the injection are subject to great variations. There may be scarcely any reaction whatsoever. At other times there are emeses, micturitions, defecations, convulsions, depression of temperature, difficult breathing, weak pulse, etc. From the study of this series of experiments it seems that neither the symptoms nor the time of death of the animals depend upon the increase in the amount or in the strength of the injected chemical, retention after ingestion (absence of vomiting), an empty stomach, or the size and weight of the animal experimented upon.

The attempt to get a series of experiments which would show a progressive increase in the severity of the pathological changes with a progressive increase in the strength and amount of injected formalin resulted in failure. Briefly summarized, the histological findings in the eleven stomachs examined are as follows:

Intense vascular congestion. Three cases which died suddenly.

Intense vascular congestion with an acute œdema of the submucosa. One case which died an hour after the injection of the formalin.

Infiltration of mucosa with leucocytes, together with positive evidences of gland cell necrosis. The necrotic material is hyaline and stains deep purple with hæmatoxylin. Two cases.

Gastritis involving the entire wall of the stomach, and characterized by marked leucocytosis, karyorhexis, and gland-cell necrosis. The necrotic material is granular and stained violet with hæmatoxylin. Two cases.

Marked leucocytosis and evidences of cell necrosis in all the tunics of the stomach, together with an intense fibrinous, hæmorrhagic exudation into the submucosa. One case.

No recognizable changes. Two cases, which were killed at the end of a month.

Twelve guinea-pigs, two rabbits, and five dogs were injected with formalin intraperitoneally. The symptoms following the injection of the chemical have fairly constant characteristics.

Post-mortem examination of the animals injected with dilute formalin shows a vascular congestion of the intestinal tract. Slight exudation into the peritoneal cavity follows the injection of 1 per cent. formalin, and this becomes extreme when the concentrated chemical is used. The intestines are contracted, and at the points of irritation variously sized ecchymoses have occurred. In the severer cases the entire thickness of the intestinal wall is soft and blood-soaked. The same is true of the omental fat and the abdominal wall. Fibrin clots are frequently found about the viscera.

Histologically we have to deal with a fibrino-hæmorrhagic peritonitis, which varies in intensity according to the strength of the injected chemical. The peritoneal-endothelial cells swell, show degenerative changes, and desquamate, singly or in plates. The muscularis shows various degenerative changes. General vascular congestion prevails, and marked leucocytic infiltration into the intestinal wall, mesentery, and abdominal wall occurs. In the severer cases fibrinous exudation and hæmorrhages of a most intense kind are common.

The lethal dose of formalin, when injected intraperitoneally into guinea-pigs, is approximately 2 cc. of 1-1000 formalin for each 100 gms. of body weight.

The injection of formalin into the lungs is followed by an exudative, fibrino-hæmorrhagic pneumonia, which varies in intensity according to the concentration of the injected formalin. Five experiments were made.

The injection of formalin subcutaneously calls forth an inflammation of the subcutaneous tissues, the most striking feature of which is an exudate which in guinea-pigs may be 3 or 4 cm. in thickness. A myositis results from the injection of formalin into the muscles. The leucocytic infiltration is mainly of the polymorphous variety.

The injection of formalin into the anterior chamber of the eye is followed by an inflammation which fills it with polynuclear leucocytes, fibrin, and a homogeneously staining serum. The same reaction follows, accompanied, however, by a conjunctivitis, when formalin is dropped into the conjunctival sac. A single drop of the concentrated formalin is

sufficient to permanently injure the eye. The course in these cases is usually as follows: Lacrimation, blepharospasm, and contraction of the pupil follow the introduction of the chemical. After twenty-four hours the pupil is contracted to pin-hole size and refuses to dilate after the use of atropine. An intense œdema of the eyelids prevents their closure, and the cornea becomes dry and opaque. Histologically we have to deal with a most intense iritis. The eyelids also show severe inflammatory changes.

Definite changes in the liver follow the injection of formalin, no matter where introduced into the body. The inhalation of formaldehyde calls forth similar changes. These consist of cloudy swelling of the liver cells, vacuolation of the cells, degenerative changes in the nuclei, slight leucocytic infiltration, total destruction of the cells, and focal necrosis.

The most severe changes were noted after the injection of formalin into the lungs or into the stomach, and after the inhalation of the vapors of formaldehyde.

The changes in the kidneys are similar to those noted in the liver.

Slight changes of a pneumonic and bronchitic character occur in the lungs of all animals experimented upon.

The spleen showed an apparent increase in the number of polynuclear leucocytes and an abundance of blood pigment.

The heart showed no changes.

An eosinophilia was found in the bladders of two dogs injected with formalin; and also degenerative and desquamative changes in the bladder epithelium.

Four animals were subjected to chronic formalin poisoning. The results of these experiments will be given later.

Formalin is either directly or indirectly positively chemiotactic. The tissues which are not infiltrated with leucocytes after the injection of formalin are those which have been so injured by the chemical that an inflammatory reaction is impossible. The leucocytic infiltration in the inflammatory reaction which follows the introduction of formalin into an

organ has these general characteristics: The eosinophiles are first to appear; these are followed by the other polynuclear leucocytes; last of all come the large and small mononuclears. The polynuclears are in all cases the predominating leucocytes. These rules also hold good in the trachea, bronchi, and lungs of animals subjected to formaldehyde inhalations. In the localized areas of pneumonia following the inhalation of formaldehyde, the mononuclears may, however, be the predominating leucocytes.

It is believed that the rapidly developing vascular congestion and œdema which follow the injection of formalin are explainable on the ground that the osmotic pressure of the injected formalin is much higher than that of the body fluids. In the attempt to establish a mean between the two, the enormous vascular congestion and œdema result. It is further believed that formalin produces the death of a cell in two ways:

(*a.*) By surrounding the cell with a fluid which has a higher osmotic pressure than the cell itself, thereby causing the abstraction of water from the cell.

(*b.*) By a deleterious chemical action upon the cell. It is this action which causes the changes in the parenchymatous organs and in the cells situated at a distance from the point of injection. From certain histological evidence it is believed that it is a reducing property of the chemical which causes the death of the cell.

SEPTEMBER 10, 1900.

OBSERVATIONS ON THE BLOOD IN TYPHOID FEVER.¹*An Analysis of the Examinations of the Blood in Typhoid Fever made in the Johns Hopkins Hospital during eleven years.*

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In connection with the third report upon typhoid fever it has been thought that it might be of interest to analyze the numerous examinations of the blood which have been made during the eleven years ending on the fifth of May, 1900. Since the opening of the hospital the blood of every case of typhoid fever has been examined microscopically. Careful counts of the corpuscles, however, have not been made in every instance, though for some years this procedure has been the rule. During this time a large number of examinations of the blood have been recorded. Doubtless a careful study of systematic observations in a more limited series of individual cases might give results of greater value than the analysis of a larger number of examinations of the blood made with less system in different cases. The records of so many observations have, however, been accumulating during the past eleven years that their classification and study seemed to be well worth undertaking.

The subject has been considered under the following divisions:

(1.) Analysis of the counts of the red blood corpuscles made during the course of typhoid fever and in the first weeks of convalescence.

(2.) Analysis of the estimates of hæmoglobin made during the course of typhoid fever and in the first weeks of convalescence.

(3.) Analysis of the counts of the colorless corpuscles made during the course of typhoid fever and in the first weeks of convalescence.

¹ Excerpt from a communication to appear in 'The Johns Hopkins Hospital Reports, vol. viii.

(4.) Analysis of the differential counts of the leucocytes made in specimens prepared according to the methods of Ehrlich, during the course of typhoid fever and in the first weeks of convalescence.

(5.) Analysis of the examinations of the blood made during various complications of typhoid fever.

Methods. — The estimates of the corpuscles and hæmoglobin were made by different house physicians, all of whom, however, were under the general supervision of the author or of Dr. Fitcher or Dr. M'Crae. Many of the early estimates were made by the author himself.

The red blood corpuscles were estimated by means of the Thoma-Zeiss counter. Toison's solution was used for dilution. As a general rule the blood was diluted in the proportion of 1:200, and a half of the entire field of the blood counter (200 squares) were counted. This was repeated several times, an average of the counts being taken.

The colorless corpuscles were counted with the same instrument, Toison's solution generally being used. With a dilution of 1:100 or 200 the entire field was counted in at least four different drops, the average being taken. Sometimes a $\frac{1}{3}$ per cent. solution of acetic acid was used with a dilution of 1:100.

In some instances the special mixer for white corpuscles was used, with an acetic acid solution of $\frac{1}{3}$ per cent., the solution being 1:20.

The hæmoglobin estimates were made with the Fleischl hæmometer.

The differential counts were made from dried cover-glass specimens stained with the triple stain of acid fuchsin, methylene green, and orange G. As most of the examinations were made in the ordinary ward routine, in a relatively small proportion was the number of corpuscles counted as great as would be demanded in a careful investigation. Generally at least 300 corpuscles were counted. None, with one exception, are included in the tables in which under 200 were recorded. In this case, where the estimate was made by a careful man, the averages of 195 elements were taken. A

considerable number or counts of under 200 corpuscles were thrown out.

The accumulation, however, of a sufficient number of estimates, based on a study of even as small a number as two or three hundred corpuscles each, cannot fail to give a more or less reliable average.

In order to obtain a better general view of the fluctuations in the average number of the different elements of the blood during typhoid fever, all these observations have been tabulated according to the week of the disease in which they were made. Two tables have been prepared in every instance, one showing the averages of all the observations made in each week, and the other, which doubtless gives a fairer estimate of the true condition, upon a basis of one count a week for each case — that is, in every instance where more than one observation was made in a given week, the average of the counts was taken and recorded as a single estimate.

In all, 265 estimates of the red blood corpuscles were made during the febrile period, and 80 during convalescence from typhoid fever; 160 estimates of hæmoglobin during the febrile period, and 52 during convalescence; 832 estimates of the colorless corpuscles during the febrile period, and 85 during convalescence. There were 116 differential counts of the leucocytes during the febrile period which were sufficiently elaborate to justify conclusions, and 28 during convalescence. A considerable number of superficial differential counts were thrown out.

In addition to these a number of observations were made in the following complications of typhoid fever: hæmorrhage from the bowels, furunculosis, phlebitis and thrombosis, pleurisy, pneumonia, severe bronchitis and broncho-pneumonia, periostitis, lymphadenitis, urethritis, cystitis, cholecystitis, parotitis, submaxillary abscess, otitis media, pulmonary tuberculosis, pregnancy, appendicular colic, peripheral neuritis, peri-rectal abscess, erythema multiforme, purpura hæmorrhagica, conjunctivitis, pericarditis, decubitus, convulsions, trichinosis (?).

A consideration of these records justifies the following conclusions:

The Red Blood Corpuscles.

(1.) A diminution in the number of red blood corpuscles becomes evident shortly after the onset of typhoid fever.

(2.) This diminution increases gradually throughout the course of the disease.

(3.) Our figures suggest that the fall in the number of red blood corpuscles may be somewhat accentuated during the fourth week of fever.

(4.) The reduction in the number of the red blood corpuscles is greatest at about the end of defervescence.

(5.) In cases of short duration, the diminution may continue into the first week of convalescence.

(6.) In longer cases, with mild persistent fever, it is not uncommon for regeneration of the blood to begin well before the end of defervescence.

(7.) The average maximum loss of red blood corpuscles in typhoid fever is about 1,000,000 to the cubic millimetre.

(8.) Considerable transient elevations in the number of red blood corpuscles per cubic millimetre may follow diarrhoea, vomiting, or sweating.

(9.) Sudden losses of a greater or less extent may be caused by hæmorrhage from the bowels.

(10.) Where the loss after hæmorrhage is severe, a certain amount of regeneration may occur during the course of the disease. In cases of long duration, however, a subsequent fall may occur.

The Hæmoglobin.

(1.) The percentage of hæmoglobin pursues a course similar apparently to that of the red blood corpuscles.

(2.) Study of individual cases suggests, however, that in instances where the anæmia has been appreciable the return to the normal point is, as in most secondary anæmias, more gradual than that of the red blood corpuscles.

The Colorless Corpuscles.

(1.) The number of the colorless corpuscles in the peripheral circulation is subnormal throughout the course of typhoid fever.

(2.) The diminution is progressive with the increase in the severity and duration of the disease.

(3.) The average number of the leucocytes per cubic millimetre at the height of the disease is about 5,000. Much lower figures are, however, common.

(4.) In cases with persistent fever there may be a tendency in the later weeks of the disease toward a slight elevation in the average number of leucocytes, as compared with that at the height of the infection.

(5.) The normal limits of variation of the number of colorless corpuscles in different cases, and in the same case, are considerable. An increase to above 10,000 to the cubic millimetre, however, is usually an indication of some foreign influence (cold baths, inflammatory complications, hæmorrhage, etc.).

(6.) Cold baths cause an immediate transient increase in the number of leucocytes in the peripheral circulation, an increase which may amount to three or four times the number before the bath.

(7.) The relative proportions of the different varieties of leucocytes one to another during typhoid fever show characteristic variations from the normal percentages —

(a.) The percentage of small mononuclear leucocytes shows at first no great change, though it is distinctly increased at the height and toward the latter part of the disease, as well as in the first weeks of convalescence.

(b.) This increase is not, as a rule, in the typical lymphocytes, but in small forms with palely staining nuclei, and a relatively large amount of transparent or nearly transparent protoplasm.

(c.) The relative percentage of the large mononuclear leucocytes increases progressively with the course

of the disease, the elevation continuing well into convalescence.

(*d.*) The increase of the largest varieties and of the transitional forms is, as a rule, not marked.

(*e.*) The elements most increased in number are cells about the size of polymorphonuclear leucocytes with pale nuclei, often scarcely larger than those of lymphocytes, and transparent or palely staining protoplasm.

(*f.*) The percentage of polymorphonuclear neutrophils diminishes progressively throughout the course of the disease, the diminution keeping pace with the increase in large mononuclear forms. The average of eight counts for the fifth week was 61.7 per cent.; of those for the sixth week, 59.2 per cent.

(*g.*) The limits of variation in the percentage of the polymorphonuclear neutrophils is considerable. Figures below 50 per cent. are not uncommon.

(*h.*) The relative proportion of eosinophilic cells in typhoid fever is diminished, the average throughout the course of the disease being under 1 per cent.

(*i.*) With convalescence the percentage of eosinophiles increases, sometimes to a point rather above the normal average.

(*j.*) In long-continued cases with persistent fever, where regeneration of the blood sets in before complete defervescence, the percentage of eosinophiles may increase to the normal average or above this, before the end of the febrile period.

(*k.*) In the leucocytosis following cold baths, the relative proportions of the different varieties of colorless elements are unaffected.

(8.) *Inflammatory complications* of typhoid fever are associated with an increase in the number of leucocytes similar to that occurring under ordinary circumstances.

(9.) It is not impossible, though our observations are insufficient to justify a positive conclusion, that the increase, in complications occurring at the height of the disease and

during convalescence, is less than that observed with similar processes occurring under other conditions.

(10.) The most extensive leucocytoses have been observed in connection with large abscesses, phlebitis, peritonitis, pleurisy, pneumonia, periostitis, cystitis, cholecystitis.

(11.) The extent of the leucocytosis depends, apparently, more upon the nature of the local lesion than upon the species of microörganism which may be its cause.

(12.) In some cases in which the complication is associated with a particularly malignant infection, especially if the patient be already in a condition of prostration, the count of the leucocytes may not only fail to show any increase, but may even reveal a tendency toward a diminution in number. In other similar conditions a slight increase in the number of colorless elements may be followed by a subsequent diminution.

(13.) *Hæmorrhage from the bowels* may be followed by an increase in the number of leucocytes which begins immediately after the hæmorrhage, reaching its maximum in from twelve to twenty-four hours. Within a week, however, the number of leucocytes generally returns to about the normal average for the period of the disease.

(14.) In some of our cases, however, hæmorrhage had no appreciable influence on the number of colorless corpuscles in the peripheral circulation.

(15.) *Perforation of the bowel* is usually followed, in a few hours, by an increase in the number of the leucocytes in the peripheral circulation.

(16.) This elevation may be considerable (above 15,000) or slight (under 10,000), and appreciable only in comparison with previous counts.

(17.) In some instances a slight increase in the number of leucocytes succeeding the perforation may tend to diminish and disappear with the aggravation of the symptoms. It is not impossible that this diminution may be the rule.

(18.) Not infrequently there is a complete absence of leucocytosis, and sometimes a diminution in the number of colorless corpuscles after a perforation.

(19.) The absence or disappearance of a leucocytosis following a perforation is an indication of the malignity of the infection or the prostration of the patient.

(20.) The prospect of relief by surgical interference is best in those cases with a leucocytosis.

(21.) A pre-perforative leucocytosis due to local peritonitis about deep ulcers may occur.

(22.) In the leucocytosis associated with the inflammatory complications of typhoid fever, especially if these occur late in the course of the disease or during the early weeks of convalescence, the relative proportions of the different varieties of colorless corpuscles may show well-marked variations from the usual figures.

(23.) These variations consist in a tendency toward the figures characteristic of typhoid fever — a diminution in the percentage of the polymorphonuclear neutrophiles, associated with an increase in that of the large mononuclear forms.

The deviation from the figures characteristic of an ordinary leucocytosis may be so marked that with over 20,000 leucocytes to the cubic millimetre there may yet be under 70 per cent. of polymorphonuclear neutrophiles.

BALTIMORE, September, 1900.

SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society; the next will be held on November 20, at the Harvard Medical School, at 8 P.M.

All communications should be addressed to the Editor,

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MAR 30 1901

JOURNAL

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OCTOBER 23, 1900.

INTRODUCTION.

J. COLLINS WARREN.

Through the public-spirited and far-sighted generosity of the late Caroline Brewer Croft, the Surgical Department of the Harvard Medical School has been enabled to undertake a systematic investigation into the origin of cancer.

The plans for this research were formulated for the first time one year ago, and a body of investigators was organized by the committee of the corporation having the matter in charge. The members of this commission have worked diligently during the past year on some of the preliminary problems connected with such an investigation, and it has been thought best at the present time to present them in the form of an annual report to the Department of Surgery. In a review of the recent investigations on the nature of cancer,¹ the head of the department has endeavored to show that the disease has been steadily on the increase during the last fifty years, a period during which the careful preparation of vital statistics has made it possible to study such a question with tolerable accuracy.

¹ Boston Medical and Surgical Journal, July 12, 1900.

Thanks to the generous aid of numerous friends who appreciate the importance of work of this character, and to the resources of a great university, we are enabled to plan these studies on a scale which it is hoped may constitute something of value towards the solution of so difficult a problem, and may stimulate others to take a renewed interest in the subject.

The work of the various men forming the commission and presented in this report speaks for itself. The Surgical Department acknowledges, with much appreciation, the assistance of the State Board of Health, for whom Dr. W. F. Whitney is at present studying the geographical distribution of cancer throughout the State of Massachusetts. It is also proper to state in this connection that Dr. J. D. Weis has been appointed to the Austin Fellowship in Surgical Pathology, and is at present in Europe, with a view of studying the nature of the blastomycetes, an organism whose name has been so much associated recently with the studies on this disease.

The presentation of this report emphasizes the policy of this department in devoting its energies, not only to the teaching of surgery, but to original research in some of the many inviting fields which are offered to well-trained and well-organized bands of scientific investigators.

STATISTICS OF CANCER.

W. F. WHITNEY.

The gross statistics have shown everywhere an increase of cancer. Those for Massachusetts have been carefully analyzed in various ways.

First, the death rate based upon the total number of deaths and the total population has been made. Second, the rate for each age period (decade) above thirty has been made. Below that age there are probably very few cases of cancer. Third, the ratio of deaths from cancer to the total number of deaths above thirty and for each age period, also to deaths other than from acute infectious diseases. In whatever way the subject was studied there was found a marked increase in the death rate from this disease.

The Massachusetts returns were also compared with those of the other New England States and Great Britain. There was a remarkable uniformity in the curves made from the report of the British Registrar General and those from Massachusetts.

The analysis of the internal forms of cancer, as far as they go, does not show any greater rate of increase than the external forms. This would tend to disprove the theory that the rate of increase is due entirely to better diagnosis, and, furthermore, it would seem that better diagnosis would have eliminated various syphilitic and tuberculous processes which formerly might have been returned as cancer.

As to locality, there does not seem to be any one portion of the State in which the disease is particularly prevalent. The studies in this regard, however, have not been completed.

I am not prepared, at present, to express any reason for this increase.

FIRST ANNUAL REPORT OF WORK ON THE ETIOLOGY
OF CANCER.

EDWARD H. NICHOLS.

(From the Sears Pathological Laboratory of the Harvard Medical School.)

The following is the first annual report to the Trustees of the Croft Fund, under the conditions of which the work upon the etiology of cancer was begun at the Harvard Medical School. Since the work is in its preliminary stage and no certain results have been obtained, no attempt has been made to draw definite conclusions from the work of this year.

A brief summary is given of the general reasons for and against the theory that cancer is due to the action of a parasite. A short review of the writings of some of the leading workers upon the subject is made, and the results of my own work are stated. A special report by each worker of this commission upon his part of the subject will follow.

General Reasons Against the Parasitic Theory.

Within recent years many men have claimed that cancer is due to the action of a parasite. When the study of the subject was begun, a year ago, especial attention was given to examination of the claims of these men.

There are certain general reasons which make it unlikely that the cause of cancer is a parasite. Cancerous tumors are composed chiefly of masses of epithelial cells. If these tumors are due to the action of a parasite, the parasite naturally must be one which causes a proliferation of epithelial cells. Most parasites and irritants produce a proliferation of connective tissue only.

Moreover, secondary or metastatic areas of cancer commonly develop in patients suffering from cancer, and may appear in organs very distant from the original focus. The metastases may appear either in tissues in which no epithelium normally is present, or in organs which have a characteristic epithelium of their own. In either case the

metastases reproduce an epithelial growth of the same type as that of the original tumor. This indicates that the secondary nodules arise from masses of epithelial cells transferred from the original tumor by means of the lymphatic or blood vessels. Since the epithelial organs in which the metastases appear have a characteristic epithelium of their own, the secondary nodules in such organs, if the proliferation were due to the action of a parasite, should consist of epithelium analogous to the epithelium of the organ in which the metastases occur.

Finally, attempts to produce cancer in animals with material from human cancer have been failures.

General Reasons in Favor of the Parasitic Theory.

On the other hand, there are certain general reasons which seem to favor the theory that cancer is due to the action of a parasite.

There is a general impression that there is a relative increase in the frequency of cancer; that is, it appears as if there were epidemics of cancer. It is difficult to see why there should be such an increase, if the etiological factor was a constant one. Certain regions also are said to have a larger portion of cancer than others, and cancer is said to attack a series of residents in certain houses.

Also, cancer extends from the original site of the disease to distant parts of the body. This extension follows the line of the lymphatics or blood vessels. In this respect the formation of metastases in cancer resembles the metastases which occur in diseases known to be due to the action of bacteria.

Finally, patients suffering from cancer often develop a general cachexia which may be entirely out of proportion to the extent of the disease. This suggests the formation of some general toxic substance, which might be due to the action of some parasite.

Special Reasons in Favor of the Parasitic Theory.

Besides these general reasons for believing that cancer is due to the action of a parasite, there are certain special reasons which have led some men to this belief.

In many cancers in the protoplasm of the epithelial cells are found certain remarkable spherical bodies which have a definite structure and peculiar staining reaction, which are believed to resemble certain unicellular organisms (protozoa, blastomycetes) which under certain conditions are known to produce definite lesions in animal or human tissues. Because of this resemblance of these bodies and because of the constant presence, as they claim, of these bodies in the cells of cancer, it is believed that they cause the proliferation of epithelial cells which results in the formation of cancer. The same belief also is held by some men who have worked along experimental lines.

The men who believe that cancer is due to a parasite may be divided into two classes:

First, those who from morphological reasons alone believe that the cancer bodies are parasites.

Second, those who have obtained from fruits or human tumors an organism which morphologically is similar to the cell inclusions of cancer, and which when inoculated into animals produces a growth analogous to human cancer.

Morphological Basis.

In 1889 Thoma (1) described certain small unicellular bodies which were frequently seen in the *nuclei* of epithelial cells of cancer. The bodies were very refractile, and had protoplasm and nucleus, sometimes a nucleolus. From their size, shape, and composition he believed them to be parasites, probably coccidia. No experimental evidence of their parasitic nature was given, and there were no drawings to show the exact morphology.

In 1890 Russell (2) described certain bodies which he had found in forty-three out of forty-five cases of cancer. The bodies were spherical, homogeneous, or hyaline, with a

refractile capsule. Russell used fuchsin as a differential stain for the bodies, which consequently have been called Russell's "fuchsin bodies." Russell claimed that the bodies were parasites, reproduced by budding, and were the cause of cancer. He acknowledged, however, that he had found these bodies in other lesions than cancer. He offered no experimental evidence in favor of his claims.

In 1891 Ruffer and Walker (3) described bodies which occurred in the protoplasm of cancer cells, occurring as spheres, having a nucleus, protoplasm, and capsule. The nucleus did not stain like the nucleus of the cell, the protoplasm was homogeneous, mottled, radiate, or granular, the capsule often was double. The cells which contained these bodies might be normal or degenerated, but never were undergoing mitosis. They believed the bodies to be protozoa.

In 1892 Ruffer and Plimmer (4) continued the work begun by Ruffer and Walker. They at first examined various types of cancer, but finally confined their examinations to cancers of the breast, because these tumors were easily manipulated and contained cell inclusions in relatively large numbers. They described bodies similar to the bodies described by Ruffer and Walker, and claimed to find them most frequently in the advancing edge of the tumor and not at all in the degenerated portions. They said that the bodies were most numerous in tumors characterized clinically by a rapid growth. The cells in which the bodies lay did not show mitosis, but the adjacent cells did. They found so-called young forms of the bodies in the nuclei of cells, from which they escaped into the cell protoplasm. In the so-called adult forms the bodies had a nucleus, protoplasm, and double contoured capsule. They believed that the body reproduced by budding or by elongation of the nucleus and fission. They gave their technic in detail and added excellent plates. These plates showed great variation in the morphology of the body. They performed no experiments to confirm their views.

In 1892 Sawtschenko (5) described various bodies in the

protoplasm of cancer cells. The bodies varied in size, form, and staining reaction. He believed the bodies to be sporozoa, and claimed that, although there were different forms of sporozoa in the same tumor, these different forms represented different stages of development of the same organism. He described a remarkable series of steps in the development of the organism. His organism as shown by the drawings does not correspond to that described by the other writers. He offered no experimental evidence in favor of his claims.

In 1893 J. J. Clarke (6) read a paper in which he claimed that psorosperms were the cause of cancer, and also claimed to find them in sarcoma. According to Clarke, two-thirds of the mass of a round-cell sarcoma was due to parasites. He also claimed to see amœboid movements of the parasites. Later he showed sections of an early scirrhus cancer containing organisms which showed amœboid movements. A committee appointed by the Pathological Society of London did not confirm his claims.

Various other writers — Foa, Soudakewitch, Vedeler, and others — have worked on similar morphological lines, and believe that the cell inclusions in cancer are parasitic and causative, but have not confirmed their opinions by isolating an organism which produces similar lesions in animals.

In reviewing the work of these writers, the different methods of technic employed make it difficult to get an exact comparison. It is notable, however, first, that the morphology of the cell inclusions is represented to vary within very wide limits by individual writers, so that one must suppose either that there are different types of organisms present, that the organism is extremely pleomorphic, or that the writers have been unable to differentiate between the organism they describe and other forms of cell inclusions, perhaps due to various forms of cell degeneration.

Second, the morphology of the cell inclusions or parasites as described by different authors does not in the least coincide, so that one must assume either that various forms of organism may produce similar results, or that the writers describe entirely different structures.

Third, different authors draw entirely different conclusions as to the location in the animal kingdom of the bodies which they describe as parasites.

Fourth, it is evident that unless it is possible to determine the nature of the parasites, and unless the bodies correspond to some similar organism whose method of reproduction is known, any claims as to the manner of reproduction of the organism must be based upon uncertain facts and cannot be determined.

Experimental Basis.

Another series of observers have seen bodies in malignant tumors similar to those already described, and, having isolated analogous bodies from fruits or from tumors, have succeeded in cultivating them upon artificial media and have inoculated them into animals with various results.

Busse (19) saw in the cells of a soft sarcoma of the tibia bodies which on fresh examination showed a clear centre and a double contoured membrane. He cultivated these bodies upon artificial culture media, best on potato, and inoculated them into the bones of a rabbit. He produced apparently inflammatory processes, but in the pus found bodies similar to those seen in the sarcoma tissue. He also produced an adhesive peritonitis when the organisms were inoculated into the peritoneum of a rabbit. In cultures the organism did not show its original double-contoured form, but the original form reappeared when inoculated into animals.

Sanfelice (7) believed that the bodies in cancer cells were blastomycetes because of their morphological resemblance. He obtained a pure culture of a blastomyces, "saccharomyces neoformans," from the juices of fruits and cultivated it upon vegetable media. He believed that the organism in the fruit juice came "from the air." He inoculated this organism into various tissues of various animals.

Guinea pigs (8) inoculated in the subcutaneous tissue died in from twenty to thirty days, and showed a nodule of "sarcoma-like" tissue at the point of inoculation with enlarged lymph nodes and white nodules in the kidney, liver, and

spleen. If the inoculation was in the peritoneal cavity a neoplastic peritonitis with enlarged mesenteric lymph nodes was produced. The lesions consisted of proliferated connective tissue. The blastomycetes were present in the lesions in enormous numbers, lying chiefly in lymph spaces. The morphology of the blastomycetes in the tissues was unlike that of the blastomycetes in pure culture, but did resemble that of the cell inclusions of cancer, and, Sanfelice claims, they have the same staining reaction.

In mice (12) death occurred in about eight days, with a general saccharomycosis and scattered nodules of proliferated connective tissue with many lymphoid elements. The blastomycetes generally were enmeshed in the tissues and not included in the protoplasm of the cells.

Rabbits (12) were more resistant. Some died in from thirty to forty-five days and showed nodules in the spleen, omentum, and kidney. The nodules showed a greater proliferation of connective tissue than occurred in guinea pigs.

He also inoculated many dogs. In some no lesion was produced, but in three cases he claimed to get an actual tumor production. His "positive" cases are three in number.

The first "positive" case (7) was a bitch which was inoculated in the breast and died after two months. The animal showed a nodule of new tissue at the point of inoculation, "like sarcoma." Inguinal lymph nodes were almost entirely replaced by similar tissue and there were similar nodules in kidney and spleen. Heart, lungs, brain, and cord showed nothing. In this tumor he saw blastomycetes sometimes in the protoplasm of the cells, sometimes free. He was unable to regain the organism on culture.

The second "positive" case (13) was a bitch inoculated in the breast with the same blastomyces which had been passed through a series of dogs. Directly after the inoculation the breast swelled, but the swelling disappeared in a few days. One month later a swelling appeared at the point of inoculation, which gradually increased, and the inguinal lymph nodes enlarged. The animal died after ten months.

At the autopsy a tumor, "adeno-carcinoma," was found affecting both of the posterior mammary glands, with similar tissue in the lymph nodes. He saw bodies which he believed to be blastomycetes, sometimes in the epithelial cells of the new glands, oftentimes free in the tissues. His descriptions and drawings show that his so-called blastomyces in this tumor does not correspond morphologically with the blastomyces as it appeared in the granulation tissue produced in other animals; the capsule, for instance, was entirely wanting. Sanfelice believes that this lack of correspondence is due to the fact that after the blastomycetes have remained in the tissues long enough they alter their shape and take a form which resembles the structures described by Russell as his fuchsin bodies. Attempts to obtain the organism by cultures on artificial media were absolutely unsuccessful. Sanfelice says that this is due to the fact that after the organism has assumed the characteristic form of Russell's bodies they will not grow upon artificial media.

In the third "positive" case (13) a dog was inoculated with the same organism in both testes. After a few weeks a tumor appeared, which involved the glans and showed a creamy discharge from beneath the prepuce. In this discharge were numerous organisms resembling Russell's bodies, but they could not be cultivated upon artificial media. The animal died after six months and at autopsy showed a tumor entirely replacing the testes, with nodules of similar tissue extending beneath the skin and involving the glans. There were large inguinal lymph nodes. Histological examination showed that the tumor was "adeno-carcinoma." There was no evidence of metastases in the internal organs or in the lymph nodes. Bodies were seen in the tumor similar to Russell's fuchsin bodies, most of them lying free, and very few in the epithelial protoplasm. Attempts to isolate the organism upon artificial culture media were absolutely unsuccessful. Animals were inoculated with an emulsion of the tumor tissue and with pus from the discharge, but as yet no positive results have been obtained.

Sanfelice inoculated other dogs (13) in the jugular veins

with the same organism. The animals became emaciated in two weeks and ultimately died. There were nodules in the kidney, and enlarged spleen and lymph nodes. The blastomycetes could be recovered on culture. The nodules in the kidney were "mesoblastic" and tended to involve the surrounding tissues, so Sanfelice says they cannot be spoken of as inflammatory, as they "do not resemble the granulomata of tuberculosis, glanders, or actinomycosis."

If dogs are inoculated in the subcutaneous tissue (13) the blastomycetes frequently produce nodules composed of proliferated connective tissue.

In cats (13) the organism produces an abscess or proliferation of connective tissue if inoculated in the subcutaneous tissue. If inoculated in the veins it produces a general infection, as in dogs.

Sanfelice also examined a primary cancer of the liver from an ox (11) and saw in fresh sections bodies like his blastomyces. He made cultures and isolated a blastomyces resembling the organism he had obtained from fruit juices, and he inoculated this organism, "*saccharomyces litogenes*," into animals. This organism has slight cultural differences from those of the neoformans. The inoculated animals showed nodules composed of young connective tissue, in the meshes of which were numerous blastomycetes.

Sanfelice believes that the parasite in cancer is due to blastomycetes and not to coccidia (12), because, although some stages of coccidia correspond morphologically to the form of the cancer bodies, other stages do not so correspond, whereas all stages of the blastomycetes do correspond morphologically to the form of the bodies seen in cancer.

Sanfelice also succeeded in isolating pure cultures of blastomycetes from human tumors and from tumors of cattle and swine (13). The blastomyces thus isolated, however, did not have pathogenic action.¹ Sanfelice states that the

¹ Wenn man nun auf solchen Platten zahlreiche Colonien von Blastomycetes findet, so kann man wohl sicher sein, dass diese von den Geschwülsten und nicht etwa aus der Luft herrühren, denn in den 5 oder 6 Stunden, während welchen die Platten der Luft ausgesetzt waren, konnten sicher nicht so zahlreiche Blastomycetes auf die Platte gelangt sein.

blastomyces so obtained come from the tumors and not "from the air." He believes that the reason blastomycetes thus isolated produce no result in animals is that the organism is acclimated to human tissues and finds the conditions in animal tissues different, and cannot produce lesions in animals until after the organism has been passed through a series of animals and become accustomed to the new conditions.

He also claims (13) that the reason he is unable to obtain cultures of the blastomyces from his experimental cancers is that the organism, after long residence in the tissues, alters its form, so that morphologically it resembles Russell's fuchsin bodies, and in this stage is incapable of being cultivated upon artificial media.

Plimmer (14), of London, of late has worked along lines similar to Sanfelice's, and has obtained results which approximately correspond. He describes bodies which occur in cancer, usually in the cell protoplasm, rarely free, which have a nucleus, protoplasm, and capsule. He has devised a differential stain for these bodies. He claims that the bodies in cancer can be seen in process of division, by budding, fission, or segmentation. He believes that these bodies are parasites because they do not react like any known degeneration, because they are not in the degenerated parts of the tumor, but in the most actively growing parts, because they are not found in normal or inflammatory tissue, and finally because they can be isolated and grown outside of the body. He has found these bodies in 1,130 out of 1,270 cases of cancer examined. In a few cases, characterized clinically by very rapid growth, he found them in enormous numbers, and he has been unable to find them in other tissues.

His attempts to reproduce cancer in animals by inoculating them with bits of tissue from human cancer have been unsuccessful.

He attempted to isolate the organisms by cultures made upon various media, and finally succeeded in his attempts by using special media and growing the organism under anærobic conditions. He believes that the isolated organism

corresponds morphologically to the bodies included in cancer cells.

He inoculated animals with this organism. Some of the animals gave no results; others showed the bodies in the tissue without any reaction. Guinea pigs inoculated in the peritoneum showed diffuse lesions in the peritoneum, omentum, and internal organs. Histologically these growths were composed of "endothelial" tissue, and Plimmer characterizes them as "tumors."

Sanfelice and Plimmer both believe that cancer is due to a parasite. Both have isolated an organism, probably a saccharomyces or blastomyces, which they claim is identical morphologically with the cell inclusions in cancer. Sanfelice obtained his organism from the juices of plants and Plimmer obtained his from a human cancer. Both have inoculated animals and have shown that the organism can live and reproduce in the living tissues. They also show that the organism may extend along the lymphatic channels, or less readily by the blood vessels, may lodge in various organs, and produce a proliferation of tissue, — practically always, however, except for two cases of Sanfelice's, a proliferation of connective tissue cells. This proliferation may be so extensive as to lead to the formation of masses or nodules of considerable size, which they call "tumors," but they do not demonstrate the histological identity of these tumors with either sarcoma or cancer. Of Sanfelice's so-called "positive" cases, the first one may be excluded, because his own description of histological appearances does not prove its identity with sarcoma, but makes it probable that he had to do with proliferated connective tissue. The two cases described in the fifth part of his series of publications upon the "Pathological Action of Blastomycetes" (13) deserve more consideration. In one case, several months after the inoculation of a bitch in the breast, a tumor developed with metastases in the lymph nodes. This case is very striking. But it must be remembered that Sanfelice had inoculated a large number of dogs, 59, at the time his article was written, without producing any result beyond the proliferation of connective

tissue. Cancer is a common disease in dogs; *e.g.*, Fröhner states that of 643 tumors of dogs operated upon at the Berliner Thierärztlichen Hochschule during the interval between 1886 and 1894, 262, or 40 per cent., were cancerous. It is possible that the appearance of the cancer of the breast, after the inoculation of the blastomyces, was a coincidence and not the result of the inoculation. Sanfelice's failure to obtain the blastomyces by cultural methods, and the fact that he says that the morphology of the organisms in the tumor was unlike the usual appearance of the blastomyces in the tissues, make one very suspicious that such was the case.

The third positive case, where cancer of the genitalia followed inoculation of the testicle, also failed to produce cultivatable organisms and Sanfelice again says that the morphology of the organism was unlike that commonly assumed by the blastomyces in the tissues. His evidence that blastomycetes were the cause of the tumor does not conform to Koch's rule — that to demonstrate the pathogenic action of any organism, that organism must constantly be present in the diseased tissues, and so distributed as to produce the results; should be isolated in pure cultures; and should, by inoculation, produce the original disease in animals. Had Sanfelice been able to isolate his organism from this tumor, his position might have been tenable. As it is, one can say that his work is valuable in the way of increasing our knowledge of the pathogenic action of blastomycetes, but that his claim that blastomycetes can produce an epithelial proliferation, and an infiltrating tumor analogous with human cancer, is not proven. His work, however, is suggestive and should be continued until absolute results are obtained.

Max Schüller (15) claims to have found unicellular organisms, probably animal, in the cells of a giant-celled sarcoma and in cancer. He describes the bodies as refractile spheres, oval or round, three times the size of a blood corpuscle, with a granular centre and a capsule. He says that the bodies have protoplasmic processes which they extrude through pores. He claims to have grown these parasites outside the

body by putting tissue from the tumor in sterile tubes at body temperature, and says his organism appears as pearl gray or yellow colonies. He has been unable as yet to reproduce tumors in animals by inoculation.

Special Reasons Against the Parasitic Theory.

In opposition to the claims of the men who believe that cancer is due to the action of a parasite is the work of other observers who, working along morphological or experimental lines, have come to entirely different conclusions.

Pianese (16), in a very exhaustive monograph, describes in detail his work upon the character of the inclusions seen in cancer. He believes that the bodies are due to various changes in the cells themselves and that the inclusions are not parasites. He devised a special technic and his article represents an enormous amount of apparently very accurate work. His work accounts not only for the typical body with a dark centre and refractile protoplasm, and a double-contoured membrane, claimed by so many to be the "parasite," but he accounts for all of the peculiar types of bodies seen in the cells and protoplasm of cancer cells. Pianese believes that these bodies arise in various ways, and that no one process explains the origin of all of them. He says that different bodies arise either from degenerations of the protoplasm, degenerations of the nuclei, atypical mitosis, or from phagocytosis. His plates are very instructive, and he apparently explains the development of the typical cancer bodies.

Dean (17) used the same technic as Russell and showed that the so-called fuchsin bodies were hyaline degenerations. He also found similar bodies in inflammatory lesions; hence he concludes that Russell's fuchsin bodies are not parasites and are not pathogenic.

Lack (18) believed that cancer formation was due to the entrance into the lymphatics of normal epithelium which, carried to the various organs, lodged and proliferated indefinitely. To test this theory he opened the peritoneum of a rabbit and scraped the ovaries so as to set free ovarian epithelium. He killed the animal after fourteen months and

found a nodule the size of a cherry attached to the uterus with disseminated nodules on the liver, mesentery, and peritoneum. The diaphragm was infiltrated with similar masses, and there were nodules in the pleura and a mass in the mediastinum. Histological examination showed the infiltrated mass to be adeno-carcinoma. This experiment is of extreme importance, because cancer in rabbits is of extremely rare occurrence. If this work can be repeated it bids fair to throw much light on the etiology of cancer.

Conclusions.

Hence we may conclude that in the cells of malignant tumors certain bodies are found, generally in the protoplasm of the cells; that these bodies are quite, but not absolutely, constantly present; that these cell inclusions vary greatly in size, shape, and color reactions with various stains. Certain observers, on morphological grounds alone, have believed these bodies to be parasites and the cause of cancer. From morphological appearances alone it is impossible to prove either that the bodies are parasites or that they are the cause of disease. One man has inoculated animals with a blastomyces obtained "from the air" and produced lesions composed of proliferated connective tissue. One man has isolated an organism, probably a blastomyces, from human tumors, has inoculated animals and produced connective tissue proliferation. In two cases, after inoculation of animals with blastomycetes, epithelial tumors have developed, analogous to cancer in men, but the evidence that these tumors were due to the action of blastomycetes is not conclusive.

Other men, on morphological grounds, believe that the bodies included in cancer cells are due to degenerative changes in the cells themselves, and that the cell inclusions are not parasitic or pathogenic. And one man in one case has apparently produced a tumor in an animal analogous to human cancer, by setting free normal epithelium.

To sum up, we can say that the theory that cancer is due to a parasite is not proven.

My own work upon the subject has been a study of a variety of tumors, in order to determine if the characteristic bodies claimed to be the cause of cancer were constantly present. A number of animals were inoculated with tissue from fresh cancer, in order to see if it were possible to reproduce cancer in animals. The attempt was made to isolate parasitic organisms from malignant tumors. Inoculation of animals with the blastomycetes of Sanfelice and Plimmer, kindly given to me by them, were made.

Morphology.

Forty malignant tumors were examined histologically. As different methods of hardening have been used by different investigators, pieces of each of the earlier tumors were hardened in a number of different fixing reagents in order to determine which method gave the best results. Absolute alcohol, alcohols of various strengths, Hermann's solution, Fleming's solution, corrosive sublimate, and Zenker's fluid were used. The best results were obtained with Zenker's fluid, and after the twenty-fifth tumor only Zenker's fluid was used.

For stains again very different methods have been used by different authors. The methods employed by Sanfelice and Plimmer were used at first. Sanfelice's method did not give satisfactory results in my hands. Plimmer's method of staining with Heidenhain's iron hæmatoxylin as a nuclear stain, and a mixture of acid fuchsin and orange G, or a solution of Bordeaux red, as a differential stain, gave fair results, but was uncertain and uneven in its results. The best results were obtained by using, at Dr. Mallory's suggestion, chloride of iron hæmatoxylin as a nuclear stain, and a mixture of 1 per cent. acid fuchsin, and a saturated aqueous solution of picric acid as a differential stain. This stain colors nuclei black, protoplasm a faint greenish pink, and connective tissue a brilliant red. Inclusions stain the central portion a brilliant red, the clear protoplasm a faint pink, and the periphery red, like the centre. The stain is easily manipulated, and is very constant and even in its action.

The technic is as follows: After hardening in Zenker's

fluid, the tissue was mounted in paraffin and cut. The paraffin was removed with xylol, followed by absolute alcohol. Corrosive crystals were removed by a weak solution of IKI for ten minutes.

The sections were then stained as follows:

1. Ten per cent. aqueous solution ferric chloride, two minutes.
2. Aqueous solution hæmatoxylin (1 to 2 per cent.), freshly made, two minutes.
3. Wash in water.
4. One per cent. solution ferric chloride until blue color is removed from protoplasm and nuclear stain is distinct (watch under the microscope).
5. Wash in water.
6. Aqueous solution ac. fuchsin one per cent., 1 part.
Saturated aqueous solution picric acid, 2 parts, two minutes.
7. Wash in water.
8. Dehydrate in 95 per cent. alcohol.
9. Xylol to clear, 3 changes, blotting dry between each change.
10. Mount in xylol balsam.

The 40 cases of malignant tumors examined included

		Cancer bodies present.	Cancer bodies absent.
Cancer of breast	16	13	3
“ “ upper jaw	1	0	1
“ “ lymph nodes	1	1	0
“ “ bladder	1	0	1
“ “ intestine	1	1	0
Secondary cancer omentum	1	1	0
Epidermoid cancer lip	3	0	3
“ “ penis	3	0	3
“ “ face	5	0	5
“ “ jaw (secondary)	1	0	1
“ “ tonsil	1	0	1
“ “ uterus	1	1	0

		Cancer bodies present.	Cancer bodies absent.
Sarcoma back	1	0	1
“ pleura	1	0	1
“ lymph nodes	1	0	1
“ finger	1	0	1
Lympho-sarcoma lymph nodes . .	1	0	1
	—	—	—
	40	17	23

Taking as typical bodies those which correspond to the description given by Sanfelice and Plimmer, *i.e.*, those which have a central portion which does not stain with nuclear stains, a more or less transparent faintly staining protoplasm, and a periphery, sometimes double, which stains sharply, it will be seen that the typical bodies are present in less than half the cases. In 16 cases of cancer of the breast the bodies were found in 13. In 5 cases of sarcoma the bodies were not seen once. In 13 cases of epidermoid cancer typical bodies were not seen. In 2 cases of cancer involving the jaw, the bodies were not present. In an epidermoid cancer of the uterus the bodies were not present in the cells of the cancer, but typical bodies were seen in epithelial cells of the mucous membrane, which showed no involvement in the cancer process.

In many of the tumors, however, in which no typical bodies were seen, other kinds of cell inclusion were seen, notably in the epidermoid cancers. These other cell inclusions occurred invariably in the protoplasm of the cancer cells, either in vacuoles or in close proximity to the nucleus of the cell. They were generally circular or oval without a definite membrane, were homogeneous or very firmly granular, and took a stain (with acid fuchsin and picric acid) of a bright pink color. They usually showed one or two dots, generally eccentrically placed, which took a nuclear stain. Sometimes no such central dot was seen.

In most of the tumors in which the typical bodies occurred they were few in number and were found only after long search. They lay usually in the protoplasm of the cells,

but occasionally were free. They were not seen in degenerated cells, but occurred in cells in which the protoplasm was well preserved. They often, however, did appear in the older part of the tumor, if the cells were well preserved. In one case one of the bodies lay in the protoplasm of a cell which was undergoing mitosis. At times several such bodies were seen in one cell; more often they were single. The number of the bodies was not greater in tumors which clinically were of rapid growth. In but two tumors were the bodies extremely numerous, and in one of these cases in some fields the bodies appeared in nearly every cell.

Inoculation of animals with tissue from fresh cancer. At first an attempt was made to inoculate animals with a bit of tissue from every cancer examined. It soon appeared, however that this was unprofitable, because of the impossibility of manipulating small tumors in such a way as to preclude the possibility of infection without destroying the tumor for histological purposes. Later inoculations were made only from such tumors as were received within two hours from the time of operation, which showed no ulceration, with its accompanying danger of septic infection, and which were of such a size as to offer certainty of aseptic manipulation.

The technic was as follows: The hands were prepared as if for a surgical operation. The tumor was incised with a sterile knife. The incised surface was seared with a heated metal, and then, with sterile forceps and small sharp-pointed scissors, a piece of tissue was removed through the seared surface and instantly dropped into the peritoneal cavity of a rabbit or guinea pig, and the wound was closed. In all, 9 rabbits and 3 guinea pigs were inoculated, chiefly with pieces of tissue from cancer of the breast. In spite of the care used, 3 of the earlier animals died of septic peritonitis, probably because of using cancer tissue which had been infected before operation. Three of the animals since have been killed at intervals of from 7 to 9 months. In one of the animals a small bit of tissue (5 mm. in diameter) was found involved in folds of the mesentery. The inoculated tissue was spherical in shape, rather soft and gelatinous, and

was encapsulated by folds of mesentery. Under the microscope the tissue is seen to be necrotic, although the outlines of the cancer cells still can be made out. There was no evidence of cancerous involvement of any of the tissues.

In one of the animals there was evidence of an old adhesive peritonitis, but no trace of the inoculated tissue could be found. The third animal showed no pathological change whatever. The other animals still are living and appear to be in good condition.

Cultures.

From many of the cases, where the cancer tissue was obtained within 2 hours of the time of operation, cultures were made by dropping a piece of the cancer, or by scraping the surface and dropping the scrapings into fluid culture media. The technic of removing the solid tissue was the same as that of removing the tissue for inoculation of animals. At first cultures were made from all the cancers; later only such tumors were used as gave certainty of manipulation without danger of septic contamination. In all, cultures were made from 13 cases of cancer of various sorts. In 3 cases, either because the tumor itself was contaminated or because of errors in technic, there developed a growth of ordinary pyogenic organisms. In the other 10 cases no growth at all developed.

Professor Sanfelice and Mr. Plimmer each kindly gave me pure cultures of the organisms with which they had obtained their results, and animals have been inoculated with cultures of each of these organisms.

Sanfelice's "*saccharomyces neoformans*" has been cultivated on various media. It grows very rapidly on any slightly acid or neutral medium which contains glucose or starch. It grows best on potato, and my experience has been that it grows more rapidly at room temperature than it does in the thermostat at 37° C.

Plimmer's organism grows very rapidly on similar media, best on potato, and better at room temperature than in the thermostat. I have not succeeded in growing it under anaërobic conditions.

A number of animals have been inoculated, of which only 5 have been thoroughly examined as yet. Several of the animals still are living.

Animal 1. Guinea Pig. — Inoculation with Sanfelice's blastomyces; .2 cc. of a 14-day-old culture of the organism in glucose bouillon were injected into the left anterior chamber of the eye. The cornea soon became cloudy. After about 10 days the eye bulged, the cornea ulcerated and finally ruptured, discharging thin pus. The eye collapsed and apparently was filled with very vascular granulation tissue. The animal was killed 7 weeks after the inoculation. At this time the eye was collapsed and showed an extensive ulcer in the middle of the cornea. Cultures were made from the blood and from the peritoneal cavity. No growth resulted. The internal organs showed no gross lesions. The axillary lymph nodes were enlarged, rather firm.

Histological examination showed that the eye was filled with very cellular granulation tissue. In this granulation tissue were many blastomycetes, generally free, but often included in the protoplasm of epithelioid phagocytic cells. The size of the blastomycetes varied within wide limits, and the morphology varied a great deal, showing what Sanfelice describes as young, adult, and degenerated forms. As a rule, the morphology of the bodies included in the epithelioid cells was quite unlike that of the cell inclusions seen in cancer cells. Rarely, however, bodies were seen which quite closely resembled cancer bodies. The staining reaction was entirely different from that of cancer bodies, the blastomycetes often remaining quite colorless, or at best taking only a very faint light pink color.

Animal 2. Rabbit. — Inoculated with Sanfelice's blastomycetes, 2.5 cc. of a fourteen-day-old culture in glucose bouillon were inoculated in the ear vein. The animal was killed seven weeks after the inoculation, at which time it had become greatly emaciated. Cultures from heart's blood and peritoneal cavity gave no growth. The internal organs showed nothing abnormal except the pyramid of the left kidney, which showed a small circular yellow area, the size of the

head of a pin. The retroperitoneal lymph nodes were rather swollen, soft, and injected. Microscopic examination of the focus in the kidney showed that the centre of the area was necrotic and infiltrated with polynuclear leucocytes. About this area was a zone of epithelioid cells in which were a few newly-formed blood vessels. In the central focus were fairly numerous blastomycetes, lying free. In the granulation tissue about the central area were much less numerous blastomycetes, generally free, occasionally in the protoplasm of the epithelioid cells. As in the first case, the morphology and staining reaction of the cells did not correspond with those of typical cancer bodies.

Animal 3. Rabbit. — Inoculation with Sanfelice's blastomycetes; 1.5 cc. of a two-weeks'-old culture in glucose bouillon was injected into the liver. At the time of the injection the syringe leaked and a few drops of the culture were spilled into the abdominal incision. The animal became greatly emaciated, and was killed seven weeks after the inoculation. The abdominal wound was healed, but in the cicatrix was a soft elastic mass 2.5×1 cm., very slightly movable. Cultures from heart's blood and peritoneal cavity gave no growth. The autopsy showed that the mass at the site of the scar was in the subcutaneous connective tissue, firmly attached to the scar. On section the nodule was grayish, rather firm, having in the centre an irregular cavity containing caseous semi-fluid material. The lymph nodes were not enlarged. Kidney and lungs appeared normal. Histological examination showed no change in lungs, liver, or kidney. The spleen was injected. The mass from the scar showed microscopically a cavity lined on one side with epidermis, the rest of the circumference being composed of epithelioid cells and young blood vessels. Surrounding the epidermis and its corium was a similar layer of granulation tissue. The cavity was filled with necrotic material and epithelioid cells with a few polynuclear leucocytes. Many of the epithelioid cells contained cell inclusions, many of which were leucocytes in various stages of degeneration. Some cells contained blastomycetes. Fairly numerous blastomycetes were seen

free. In the epidermal cells along one side of the cavity were occasional blastomycetes, generally free; rarely did they appear to be in the protoplasm. No mitotic figures were seen in the epithelial cells, and there was no evidence of cell proliferation. Kidney, liver, lung, and lymph nodes showed no change. The area was practically an abscess cavity surrounded by a thick layer of granulation tissue. The epithelial cells probably were due to infolding of the edges of the skin incision.

Animal 4. Guinea Pig.—Was inoculated with Plimmer's organism; 1 cc. of a glucose bouillon culture was injected into the abdominal subcutaneous tissue. The animal was killed five weeks later, and was much emaciated. On the left side of the abdominal wall was a nodular swelling 2 X 3 cm., firm, indurated, not freely movable. Inguinal lymph nodes on both sides, especially the left, were enlarged. Cultures were made on potato and in glucose bouillon. Pure cultures of the original organism were obtained after three days. On section the tumor was seen to consist of rather œdematous tissue forming a discrete mass outside the abdominal wall, but firmly attached to and infiltrating the underlying muscles. The line of demarcation between the nodule and the abdominal wall was distinct, however. The infiltration of the abdominal wall formed a flattened swelling, which pushed up the peritoneum and projected into the abdominal cavity. There was no evidence of metastases in the peritoneal cavity. The retroperitoneal and inguinal lymph nodes were enlarged, and on section were composed of tissue closely resembling the chief nodule. Lungs, liver, and kidney appeared normal. Spleen and lymph follicles were enlarged. The microscope showed that the chief nodule was composed almost entirely of proliferated connective-tissue cells, with, in places, relatively numerous newly formed blood vessels. The blastomycetes were present in this granulation tissue in enormous masses. They lay usually free in meshes of the connective tissue. Many of the bodies, however, were included in phagocytic cells, sometimes one, sometimes several bodies being included in one such cell. The muscle fibres

of the abdominal wall had largely disappeared; the bundles of muscle which remained showed vacuolization and degeneration, but there was no evidence of invasion of muscle fibres by the blastomycetes. In places was considerable infiltration of the granulation tissue with polynuclear leucocytes. The lymph nodes were enlarged and the lymphoid elements had been almost entirely replaced by granulation tissue like that in the chief nodule, in which there were very numerous blastomycetes. Lymph sinuses were dilated, and contain very numerous blastomycetes, some free and some contained in phagocytic cells. In the spleen were numerous circular and irregular nodules of similar tissue containing blastomycetes. Liver was normal. In the kidney, chiefly in the cortex, were small circular nodules of granulation tissue containing blastomycetes. The lungs showed microscopic areas of the same. The morphology and staining reaction of the blastomycetes do not correspond to those of typical cancer bodies.

Animal 5. Guinea Pig. — Inoculated with Plimmer's organism, 1 cc. of a glucose bouillon culture 18 days old, in the peritoneal cavity. The animal was killed three weeks later. The animal was emaciated, and showed in the abdominal wall at the point of inoculation a firm circumscribed nodule, 1 cm. in diameter, quite firmly attached to the skin. The inguinal lymph nodes were enlarged. The peritoneal cavity looked normal, and there was no especial increase of fluid. The mesenteric and retroperitoneal lymph nodes were enlarged, and on section appeared firm, and pale pink in color. The liver showed no gross lesion. The kidney showed in the cortex numerous small circular areas like tubercles. Similar nodules were seen in the spleen. The lungs were injected, and seemed rather firmer than usual.

On microscopic examination the lungs showed numerous small irregular nodules composed of proliferated connective-tissue cells with a few new blood vessels. The nodules appeared to arise from the connective tissue of the alveolar walls. Blastomycetes were numerous in these nodules, usually free, sometimes included in the protoplasm of large

phagocytic cells. The blastomycetes could be seen budding in places. In parts of the granulation tissue eosinophilic leucocytes are numerous.

The kidney showed similar nodules chiefly in the cortex, affecting only the connective tissue between the tubules. There was no proliferation of renal epithelium, nor were there blastomycetes seen in renal epithelium.

The liver showed no areas of proliferation.

In the spleen were nodules like those already described, which appeared generally in the lymph follicles.

In the lymph nodes the lymphoid tissue was largely replaced by proliferated connective-tissue cells, partly as rather dense bands, partly as a loose mesh-work in which blastomycetes were lying in large numbers. In places this connective tissue was necrotic, and infiltrated with polynuclear leucocytes. In some lymph nodes much of the lymphoid tissue remained, and the blastomycetes were chiefly in the lymph sinuses, either free or in the protoplasm of epithelioid cells.

The nodule in the skin was confined to the corium, and did not involve the epidermis, which showed no sign of proliferation. The blastomycetes in this nodule were practically entirely free.

The staining reaction and morphology of the blastomycetes in the experimental nodules did not correspond to those of typical cancer bodies.

The most of the work of the year has been largely preliminary, and is not sufficiently advanced to enable me to draw definite conclusions. Typical cancer bodies have been found generally present in certain types of cancer.

They never have been found in epidermoid cancer. Attempts to produce cancer in animals by inoculating them with bits of tissue from human cancer so far have uniformly failed. No attempt to isolate an organism from human cancer has succeeded. Inoculation of animals with the organisms of Sanfelice and Plimmer has resulted in the formation of nodules composed of proliferated connective-tissue cells and newly formed blood vessels (granulation tissue),

but no tumor resembling cancer of human beings has been produced.

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[illegible]

PLATE I.

Cell inclusions in protoplasm of epithelial cells from adeno-carcinoma of breast.

Stained with iron hæmatoxylin, acid fuchsin, and picric acid.

Camera lucida.

FIGURE 1. — Zeiss comp. oc. 8; apochromat. 2. mm. : apert. 1.30.

FIGURE 2. — Zeiss comp. oc. 6; apochromat. 4. mm. : apert. 0.95.

FIGURE 3. — Same as 2.

FIGURE 4. — Same as 1.

Fig. 1



Fig. 2



Fig. 3

PLATE II.

FIGURE 1. — Same as in Plate I., — Figure 1.

FIGURE 2. — Same as in Plate I., — Figure 2.

FIGURE 3. — Same as in Plate I., — Figure 3.

FIGURE 4. — Cell inclusions in protoplasm of epithelial cells from adenocarcinoma of breast.

FIGURE 5. — Cell inclusions in protoplasm of epithelial cells from adenocarcinoma of breast.

FIGURE 6. — Cell inclusions in protoplasm of epithelial cells from adenocarcinoma of breast.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

Fig. 5

Fig. 6

PLATE III.

Guinea-pig inoculated with Plimmer's organism, killed after four weeks. Skin is reflected. Right abdominal wall and abdominal viscera are removed. Left abdominal wall in situ, and shows nodule of granulation tissue just to the left of the median line. Nodule infiltrates entire thickness of the abdominal wall. Chain of enlarged lymph nodes extends from the nodule into the inguinal region.

Fig. 1

ON THE PRESENCE OF THE SO-CALLED "PLIMMER'S
BODIES" IN CARCINOMA.

R. B. GREENOUGH.

(From the Clinical Pathological Laboratory of the Massachusetts General Hospital.)

This work was taken up in October, 1899, under the direction and with the assistance of Doctor Nichols, for the Department of Surgical Pathology. Doctors Whitney and Wright, of the Massachusetts General Hospital, kindly put their material at my disposal, and this report is based upon the results of the examination of twenty-one cases of carcinoma, nineteen of which were cases of carcinoma of the breast.

The method of examination was as follows: The material was taken, as a rule, directly from the operating room, and a record kept of the precise anatomical locality from which the specimens were removed. A rough chart of the area involved was preserved in most of the cases and the tissues from each area were separately fixed and hardened. Where material was sent into the laboratory the topographical relations were obtained as well as they could be made out, and a record kept in these cases also.

Fixation.—As previous experience had shown that Zenker's fluid was more satisfactory than Hermann's as regards the staining character of the tissues, no attempt was made at first to use Hermann's fluid, although the latter is recommended by Plimmer himself as the best fixation fluid.

Later in the year, however, a second attempt was made with Hermann's fluid and with perchloride of mercury, but again with no obvious advantages over Zenker's fluid. It is to be regretted that in this matter of fixation Plimmer's recommendations could not be carried out, but the results with Hermann's fluid were so universally unsatisfactory that no reliance could be placed upon the action of the fixed tissues to the stains.

Hardening.—After twenty-four hours in Zenker's fluid

distinguished from other structures which are not claimed to be parasites.

Two cases of carcinoma, one of the peritoneum, the other an epithelioma of the nose, were also examined in this series of cases, but without results. The peritoneal cancer, having origin, in all probability, in the ovary, was not well fixed. The other — the epithelioma — was fixed perfectly and yet showed no bodies.

In addition to the series of cases here presented, which were examined after October, 1899, there are the results of the examination of 7 other specimens of carcinoma, which were fixed and stained by these same methods, and can properly be added to the above list, although the work was done prior to the beginning of the present work.

Of this series there were four cases of breast cancer, in all of which the bodies could be demonstrated, and in one of which, a scirrhus type of cancer, they were very numerous. One case of Paget's disease of the breast was also examined, where obvious cell inclusions were present, but nothing which could be properly likened to the characteristic Plimmer's bodies. There was also one carcinoma of the ovary, in which the typical bodies were numerous, and one epithelioma of neck, in which no bodies could be found. Adding these cases together and summing up briefly the results:

1. The appearances known as "Plimmer's bodies" were found in each of 23 cases of breast cancer.
2. They were more numerous in the periphery of the tumors, and in the metastases.
3. They were not found in areas which had undergone even slight degeneration, whether before or after removal.
4. They were more numerous in the slow-growing carcinomata, and less frequently found in the rapidly growing ones.
5. They were more numerous in scirrhous than in medullary or adeno-carcinoma types of cancer.
6. They were not found in three cases of the epithelioma type (one of which was a typical Paget's disease of the breast).
7. They were present in one case of ovarian carcinoma, and absent in another case of general peritoneal cancer, of probable ovarian origin.

PLATE IV.

FIGURES 1, 2, 3. — Sections of carcinoma of breast. Single cells containing typical "Plimmer's bodies."

FIGURE 4. — Single carcinoma cell containing a body with large central staining area and a sharply defined periphery.

Fig. 1.

Fig. 2.

Fig. 1.

Fig. 1.



PLATE V.

FIGURE 1. — Single carcinoma cell containing a body in which the central staining area presents the appearance of budding.

FIGURE 2. — Single cells containing typical Plimmer's bodies.

FIGURE 3. — Large carcinoma cell with numerous vacuoles, resembling "parasite spores."

FIGURE 4. — Carcinoma cell containing two bodies of different sizes suggesting a growth by budding.

The photographs were prepared by Mr. L. S. Brown in the Laboratory of the Massachusetts General Hospital. The lenses used were Zeiss Apochromatic 3 mm. $\frac{1}{6}$, with a No. 4 Projection Ocular, and give an amplification of about 1000 diameters. The specimens were procured from cases of breast carcinoma.

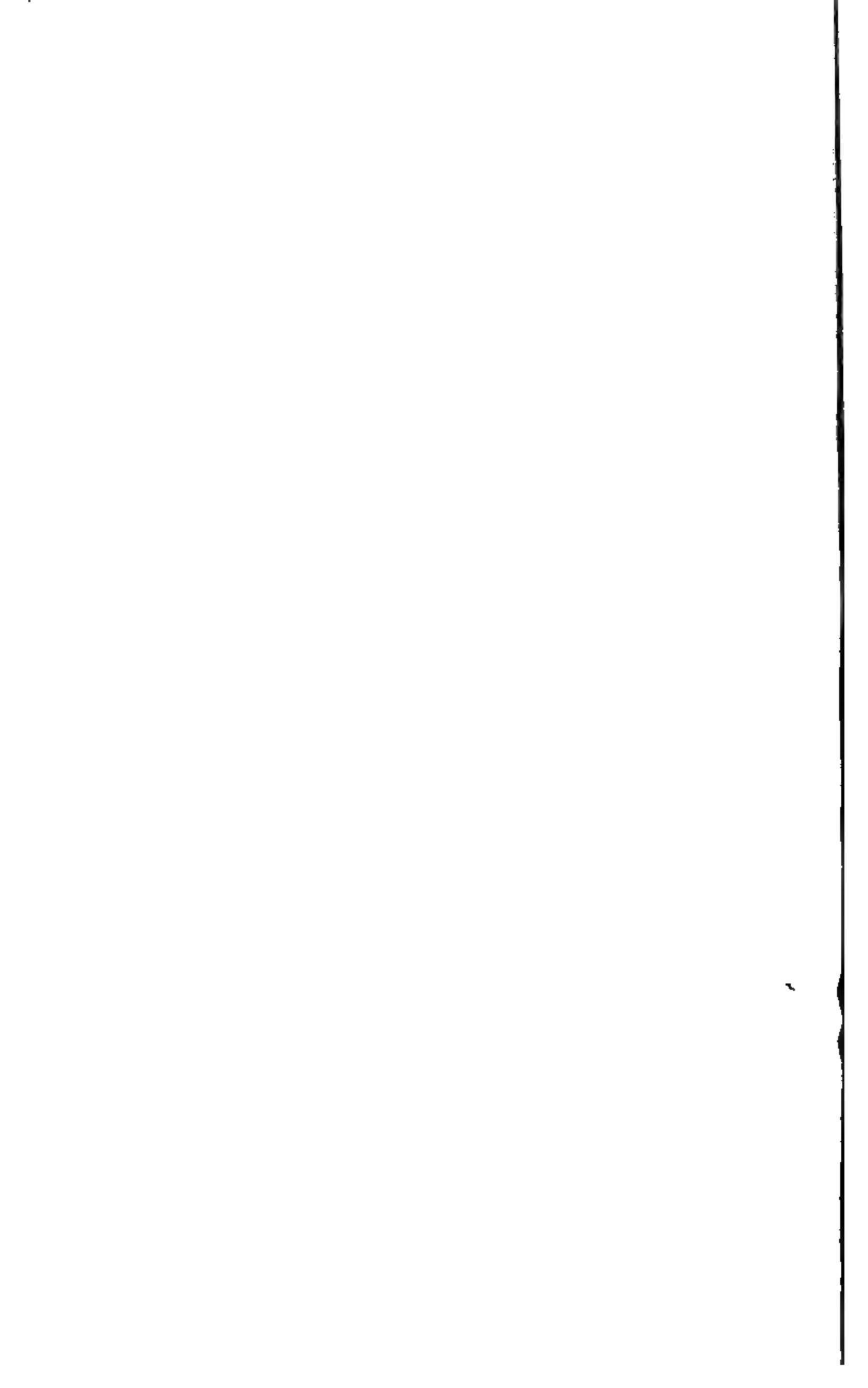
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Fig. 1

Fig. 2

Fig. 3

Fig. 4



TUMORS AND SPOROZOA IN FISHES.

E. E. TYZZER.

In this paper I shall try to give, in brief, a few facts concerning the sporozoa that infect fishes. In addition to this, I shall present a species which I found, and which I believe has never been described. Although it may seem to have little bearing on the etiology of cancer, it may, however, be of interest to you to know where this class, sporozoa, belongs in the animal kingdom — what these organisms are like, and what their life history.

I wish to state in the beginning that but few of the general facts concerning these organisms are of my own observation, but are taken largely from the monograph of R. R. Gurley, M.D., of the United States Fish Commission. In classification I have followed Delage and Hérouard in their work on "The Protozoa."

In considering the branch protozoa, we find it divided into four classes: the rhizopods, the flagellates, the infusoria, and the sporozoa. The sporozoa are unicellular, ameba-like organisms, destitute of appendages (such as cilia or flagella), which multiply by spore formation, and which are invariably parasitic. They possess no pulsating vacuole, as do many of the amebæ. Of all the class sporozoa, the myxosporidia form the only group, so far as is known, that infects fishes. Besides fishes, the myxosporidia are also found with the crustacea and certain of the insects. They may be found in practically any of the tissues or natural cavities of their host. The individual species, however, seem to infect certain tissues or cavities in preference to others.

In the life history of the organisms there are two well-defined stages: the myxosporidium stage and the spore stage. The young myxosporidium, after it is "hatched" from the spore, is a very active, irregular, ameboid, or vermiform organism, generally possessed of two nuclei. It at once penetrates a cell of its host's tissues — perhaps an epithelial cell or perhaps a red blood cell. Now follows a period of

growth in which the organism distends and at last bursts the cell which has harbored it. On becoming free, the myxosporidium continues to grow and the nuclei multiply, division taking place by mitosis. As it increases in size the movements are less active and the nuclei are scattered throughout the whole organism. It is at this stage ready for sporulation. Before describing this process it would be well to describe the spore.

With each species the spores are characteristic, and thus it is by the spore rather than by the adult ameba that the myxosporidia are classified. The myxosporidium or ameba stage may be indistinguishable in species that are quite unlike in the spore stage. The typical spore, let us say, consists of several parts, one essential and other accessory parts. The essential portion is the "sporoplasm," which is in time to develop into the perfect ameba. The sporoplasm always contains one or more (usually two) nuclei, and it occupies a position in the spore which is called arbitrarily "posterior." The accessory parts are those concerned in the "capsules," which are situated at the end opposite the sporoplasm, or "anterior" extremity of the spore. These capsules are highly refractile and are continuous with a duct opening anteriorly on the spore. They each enclose a coiled thread-like body, or "filament," which under certain conditions is extruded through a duct opening on the surface of the pore. The filaments execute active movements, which may result in the movement of the entire spore. This apparatus, consisting of capsule and filament, bears a striking resemblance to the nematocysts of the coelenterates. Their function, however, cannot be such. A great many theories have been offered as to the function of these filaments. Observations on this subject are so unsatisfactory that not much information has been gained. It is certain, nevertheless, that some spores are slowly propelled by the action of the filaments. The census of opinion is, that they are organs either for the attachment or for the dissemination of the spores. The surface of each spore is composed of a thick "shell," which may be bivalved or otherwise. In certain species the

shell is drawn out posteriorly in a long, tapering process, the "tail."

To go back to the process of sporulation: around each of the many nuclei of the adult myxosporidium a mass of clear protoplasm is differentiated. This mass, with the included nuclear material, is termed the "pansporoblast." At the periphery of this there is a delicate surrounding membrane. Each nucleus divides and subdivides by mitosis until the pansporoblast contains perhaps a dozen nuclei. The mass divides subsequently into two equal parts, the "sporoblasts," each containing three nuclei. The remainder of the nuclei take up their position with the membrane surrounding the mass. Each sporoblast now consists of unequal parts, one large and two small, each containing a nucleus. The larger part ultimately forms the sporoplasm and takes up the larger part of the spore; the two smaller parts are concerned in the formation of the capsules. The capsules first appear as transparent vacuoles. Into these project little "buttons" of protoplasm, which elongate, are pinched off at the base, and finally become filaments. These are coiled within the capsules, which are now possessed of a definite membrane. In the above manner the whole substance of the myxosporidium may be converted into spores.

The spore stage with the myxosporidia does not so much represent a period of rest as it does one of multiplication and dissemination. Another question is: "How do the spores gain entrance to the host?" Such localities as the gills, the alimentary canal, the skin, and the urinary bladder have been mentioned by various observers as probable points of entrance. It is probable that the different species elect different points, and it is possible that, in the more general infections, the spores are spread throughout the body by way of the blood and lymph channels.

Pathology.

As a matter of fact each species develops its own characteristic pathological process. The tissues of the fish as a rule react but slowly, but there are described, nevertheless,

epidemics in which the processes have gone on so rapidly that the fish soon succumb and that too in large numbers. In all the literature upon this subject I have nowhere found described a neoplasm such as is ordinarily designated a tumor; nor have I found evidence of proliferation of epithelium in any case. In the lake-pike, a round-celled sarcoma is described by Ohlmacher, but he found no organisms, although he had personally examined many preparations of the myxosporidia. This tumor, which he described, started apparently in the connective tissue near the vertebral column, and metastases were found throughout the mesentery and involving many of the viscera.

A New Species of Myxosporidia.

I will now describe an organism which I found infecting several different species of fishes. My attention was first called to a diseased condition of the muscles of young herring by Dr. Linton. He had observed this condition a year previous, but had not investigated the matter. Examination of the fish showed small white cysts, one to two millimeters in length, lying between the muscle fibers of the myotomes. (See Plate VI., figs. 1, 2, and 3.) With a little pressure the cyst contents—a white, creamy mass—was squeezed out. Under the microscope this substance proved to be made up of small quadrilateral spores. Alewives and other fish were also found to be infected quite commonly with the same organism.

The spores are quadrilateral when seen face on, and in profile are oval. The four corners are a little protuberant and are directed slightly forward. The spores vary little in size, averaging about seven to seven and a half μ in breadth. In a given fish there was but little variation in shape, but as they were afterwards found in several species of fishes, the shape varied considerably. Thus in the young scup the corners were so drawn out as to give the spore an almost stellate appearance. There is also a tendency of the spores to occur fitted together in clumps of four or eight. (See fig. 6.) Each spore contains four capsules, very delicate, pale green in color, radiating from the anterior extremity toward the four

corners. (See fig. 5.) From the four capsules were extruded, at times, the four filaments, whose vibrations caused the spore to move gradually forward. After a time the filaments would shorten and ultimately return into the capsules. Each capsule is surrounded by a clear space, the "perivesicular space." The remainder of the spore is taken up by the sporoplasm, and the whole surrounded by the shell. Four furrows radiate from the anterior extremity outwards to the sides, causing the spore to appear quartered. Posteriorly there lies an oval body, the nature of which I have not yet been able to make out with certainty. It takes a nuclear stain and it may be justifiable to consider it a "macronucleus" belonging to the sporoplasm. The spore ends anteriorly in a little projection through which the filaments pass.

The spores are stained by the ordinary aniline dyes, but the nuclei stain with difficulty. It is most satisfactory to use such stains as carbol fuchsin, or Loeffler's methylene blue, followed by a decolorizer. The capsules stain readily but are as readily decolorized. With acetic acid the filaments are extruded and become fixed and the four nuclei at the corners are brought out.

In examining many different species of fishes, they were found in the alewife, the scup, the herring, the menhaden, the hickory shad, and the cunner—in all, six different species. In these the young fish were most commonly infected. It is probable that this percentage would have been increased if a more careful examination had been possible. In old fishes the tissues seem to be getting the better of the spores, and the latter were found to be quite degenerated. Owing to the difficulty of keeping a census of the sea, I can give no opinion as to the mortality of the infected fish. When kept in an aquarium they seem to thrive well until something more serious happens to them.

In studying sections of the tissues of small fishes, cysts were found so small that they were not discernible to the naked eye, yet no earlier stage of the organism could be found. There are cells which at times include one or more of the spores, and whether these are sporoblasts or phagocytic cells

I cannot say. They have every characteristic in common with certain cells found in the blood, having a lilac-stained protoplasm, and an irregular nucleus situated invariably at one side near the periphery of the cell. There is at times a definite cyst-wall composed of connective tissue, and at other times none. The connective tissue may grow among the spores inmeshing them in a network.

This spore seems without doubt to belong to the myxosporidia. Its mode of encystment, however, resembles that of the sarcesporidia which are found in the domestic animals and some birds. How the cysts increase in size, as they certainly do, with the growth of the fish, remains a mystery. This is not the first instance in which the development of such organisms cannot be followed. In a case similar to this, one observer suggested that the sporoblast existed free from any form of ameba and independently went on with the process of sporulation.

PLATE VI.

FIGURE 1. — Small cysts in a young menhaden.

FIGURE 2. — Larger cysts in a young herring.

FIGURE 3. — Cyst in which the connective tissue is enmeshing the spores — scup.

FIGURE 4. — Smear stained with carbol fuchsin — scup. The nuclei and capsules have both retained the stain.

FIGURE 5. — Smear stained with Loeffler's alkaline methylene blue — alewife. The capsules are darkly stained.

FIGURE 6. — Smear showing characteristic clumped arrangement of the spores. Nuclei dark, capsules light.

Fig. 1

Fig. 2



Fig. 3

Fig. 4



Fig. 5

Fig. 6

THE RECONSTRUCTION IN WAX OF A NODULE OF CANCER.

EDWIN A. LOCKE.

The following work was undertaken at the Sears Laboratory during the present year at the suggestion and under the personal direction of Dr. Nichols. To Dr. Mallory I am also indebted for many valuable suggestions.

My aim has been the construction in wax of an exact model, on an enlarged scale, of a minute portion of the growing edge of a carcinoma. Together with a careful microscopical study of a series of sections, this work in the study of the general morphology of cancer was undertaken in the hopes that it might throw some light upon the general theories of the course of the growth. Besides emphasizing certain things shown by microscopical examination, it was hoped that it might make evident some new features of the growth. While obviously impossible in such a model to show the cellular structure, it is, if reasonable skill and care in technique be exercised, a comparatively easy task to reconstruct with almost absolute accuracy the columns and masses of cells.

The method followed is the so-called "Reconstruction Method of Bom," so long used in embryological studies. This consists (1) in the cutting of the tissue into serial sections, (2) the drawing of these sections on paper with a definite magnification, (3) the transferring of these drawings to wax plates, (4) the cutting of these plates in accordance with the drawings, (5) the piling up of the wax into a model, and (6) finally the fusing of the plates.

A small portion of the growing edge of a scirrhus cancer of the breast was taken, fixed, and hardened in Zenker's fluid, imbedded in paraffin, cut in serial sections $\frac{1}{100}$ mm. in thickness, and stained with methylene blue and eosine. In this series I was able to follow in 74 consecutive sections one part of the growth from its outer limits to its point of division from the main tumor. It appears as a collection of many columns of cells closely surrounded by very dense connective

tissue not unlike a capsule. The space between the capsule and the tumor is occupied by a loose connective-tissue containing a few blood-vessels, and densely infiltrated with leukocytes. This I selected as offering the best opportunity for the reconstruction method. For this purpose it was necessary to draw on paper the sections of a camera lucida, a uniform enlargement of the original being arbitrarily taken. The sharp difference between the capsule and the surrounding fibrous stroma was traced. With the completion of each section a drawing was placed in the field in such a position that manipulation of the mechanical stage, through the microscope, exactly fitted the drawing. Then after drawing the capsule, the projection could be drawn, and the drawing adjusted to it in a similar manner. This method secured a uniformity in the drawings, and consequently a standard by which to build up the tumor.

The next step consisted in the transformation of the drawings into lines, by means of carbon tracing-paper of proper thickness. The thickness of the tracing-paper with its diameter and that of the drawing were taken into consideration in determining the required thickness of the plates. These plates could be made of wax. These plates were of pure wax, and made by the following method: A large pan 24 by 14 inches was filled with water and placed on a water bath in which it could be heated or cooled at will. When the temperature of the water a few degrees above the melting point of wax, a given amount of molten wax was poured into the water, it rose to the surface and assumed an absolutely level surface. A Bunsen flame applied to the surface of the wax drove out any bubbles present. Rapid cooling was effected by immersing the wax into cold water. When sufficiently solid, they were cut into the designed sizes. Previous to the construction of the model, each one was cut out according to the drawing made. With the addition of each layer, the model was built up, masses representing cross-sections of the tumor were held in place by the insertion of pins, about 1 cm. in length heated moderate

PLATE VII.

Lateral view of wax model of a small nodule from the edge of a scirrhous breast cancer with an enlargement of 102 diameters (or volume 1,061,208 times the original).

Model represented in cut one-eighth natural size.

A. — Tumor.

B. — Space occupied by the fibrous stroma.

C. — Fibrous tissue of the breast.

ence to the sections under the microscope served as a check both to the fitting of the layers and to the subsequent fusing. The layers in every case fitted almost perfectly, a sufficient evidence, it seems to me, of the accuracy of the work. Finally, by means of a small moulding-iron heated in the flame, the layers were fused into a solid mass.

The model thus constructed represents only the beginning of the study undertaken, and from this alone clearly no general conclusions can be drawn. Its value lies chiefly in the illustration which it gives of the relation of various parts and the character and manner of growth. More clearly than by any other method it demonstrates the alveolar character so typical of carcinoma. Nowhere did I find nests of cells which sooner or later did not unite with other portions of the tumor. Each column is an outgrowth. These columns are very irregular, extremely variable in size, and appear to have no general law governing their direction. A single small clump of cells may within the limits of a few layers become a complicated mass, honeycombed by bonds of connective tissue and growing in many directions. In many places the outgrowth ends abruptly, indicating that the cancer may extend by mere expansive growth as well as by infiltration.

REPORT OF CULTURE/ EXPERIMENTS MADE WITH
CARCINOMATOUS TISSUE, 1899 AND 1900.

OSCAR RICHARDSON.

(*Clinico-Pathological Laboratory, Massachusetts General Hospital.*)

These culture experiments were made to demonstrate whether the bodies found in the cells of carcinomatous tissue could be grown or not. The investigation was made parallel to one by Dr. R. B. Greenough on the pathological histology of the same material. The material was obtained chiefly from the surgical departments of the Massachusetts General Hospital and the tissues were taken and the cultures made as soon as possible after the time of operation. This procedure insured a fresh clean warm tissue in most instances and gave the most favorable conditions for making cultures.

The cultures were made under the strictest asepsis, all instruments and the glass plate on which the piece of tissue rested while the culture was made being cleaned in the Bunsen burner flame. The cube of tissue was seared on all its surfaces and an opening made into the central portion of the mass from which the cells of the new growth were curetted out as a semi-fluid pulpy mass in which the tissue cells were freely liberated. This material was then directly placed in sterilized tubes of media of various kinds and under aërobic and anaërobic conditions to be described.

Media.

Carcinoma Bouillon.—The tumor mass was taken from the breast and stripped of as much fat as possible. A few pieces of muscle clear of all fat were included. This material was chopped finely, weighed, and made up in the same proportions as ordinary bouillon. Then it was boiled thoroughly and filtered and brought to a boiling condition again, when peptone and salt were added as in ordinary bouillon. It was next carefully neutralized and boiled again for a short while and while hot, 2 per cent. of glucose and 1 per cent., of tartaric acid added. Then it was allowed to cool in a flask, then

boiled again and filtered and tubed hot. The tubes of the culture medium were then sterilized in the Arnold sterilizer three times, one half hour each time. When a tube was to be inoculated it was sterilized for one half hour just before inoculation.

Blood Serum, Plain Bouillon.—Prepared according to directions in Mallory and Wright's "Pathological Technique."

Bouillon.—Made like plain bouillon mentioned above, except that in place of beef the tissue from a cystic breast was used.

Bouillon and Agar.—Made from the mucosa of the intestine of a hog at the suggestion of Dr. Warren.

The small intestine of the hog was taken in fresh condition without cutting and washed thoroughly with running water until the water ran perfectly clear. The intestine was then laid open and the mucosa scraped off with a glass slide. One hundred and fifty gms. of mucosa were easily obtained from the small intestine of one hog.

Agar.—250 c.c. of the mucosa was taken and 500 c.c. of distilled water was added. This was boiled for one half hour. It was then allowed to cool, was boiled again, then neutralized and boiled again. After filtering, it was boiled and 5 gms. of peptone and $2\frac{1}{2}$ gms. of salt added and the material was then neutralized again and the boiling continued for twenty minutes and it was then filtered. One-half of this bouillon was then taken and $1\frac{1}{2}$ per cent. of agar added and the medium boiled until the agar was dissolved. It was neutralized (if necessary) and then cooled to 68 degrees C. A well-beaten egg was then added and the medium boiled until the egg thoroughly coagulated. It was then filtered, tubed, and sterilized by the fractional method, then slanted.

Bouillon.—The other half of the bouillon was tubed and sterilized by the fractional method.

In one or two instances the tissue from a normal breast and from normal lymphatic glands was placed in sterile tubes of media and inoculated with cells from carcinomatous tissue.

Again, pieces of the tumor with adjacent tissues were placed in sterile tubes without the addition of any other

medium. In one or two cases the blood from the adjacent tissues of the tumor mass was added to the medium inoculated with the carcinomatous cells.

Methods of Cultivation.

Aërobic. — The usual test tube method, the carcinomatous tissue being distributed in or on the medium.

Anaërobic. — Fluid cultures were made after the method of Dr. J. H. Wright described in the "Centrabl. f. Bakt. u. Parasitenk," January, 1900, and the "Journal of the Boston Society of Medical Sciences," January, 1900.

Solid cultures. The test tubes, after inoculation, were placed in a sealed jar containing pyrogallic acid, according to Buchner's method.

Sub-cultures. With some of these the plate method of Petri was used. The records of the details of the culture experiments are to be found in the following table:

	1899.	CARCINOMA BOUILLON.		PLAIN BOUILLON.
		Aërobic.	Anaërobic.	Aërobic.
Carcinoma lymphatic glands with involvement of the humerus. }	July.	Negative.	Negative.
Carcinoma lymphatic gland. Dr. Conant. }	Aug. 4.	Negative.
Carcinoma lymphatic gland.	Aug. 5.	Negative.
Carcinoma breast. Periphery growth. Dr. Elliot. }	Aug. 10.	Negative.
Carcinoma of breast. Periphery growth. West surgical department. }	Aug. 20.	Negative.
Carcinoma of breast. Culture from gland. }	Aug. 24.	Negative.
No. 1. Carcinoma breast. Cultures from periphery and centre of tumor and from axillary gland. Dr. Mixter. }	Sept. 30.	Negative.
Carcinoma breast. Periphery growth. Dr. Warren. }	Oct. 4.	Negative.	Negative.
No. 2. Carcinoma breast. Periphery of growth. Dr. Warren. }	Oct. 6.	Negative.
Carcinoma breast. Periphery growth. Dr. Warren. }	Oct. 9.	Negative.	Negative.

	1899.	CARCINOMA BOUILLON.		PLAIN BOUILLON.		BLOOD SERUM.	
		Aërobic.	Anaërobic.	Aërobic.	Anaërobic.	Aërobic.	
No. 3. Carcinoma breast. } growth. Dr. Warren.	Oct. 19.	Negative.
No. 4. Carcinoma breast. } growth. Dr. C. B. Porter.	Oct. 25.	Negative.
No. 5. Carcinoma breast. Periphery of growth } and gland. Blood from tissues of breast } added in all cultures. Dr. C. B. Porter.	Oct. 27.	Negative.	Negative.	Negative.	Negative.
No. 6. Carcinoma breast. Periphery of } growth. Dr. C. A. Porter.	Nov. 7.	Negative.
No. 7. Carcinomatous peritonitis. From } fluid. Dr. Warren.	Nov. 7.	Negative.	Sterile.
No. 9. Carcinoma breast. Periphery growth. } Dr. Warren.	Nov. 16.	Negative.
No. 10. Carcinoma breast. Periphery growth. } Dr. H. H. A. Beach.	Nov. 20.	Negative.
No. 11. Carcinoma breast. Cheesy matter } tumor. Dr. C. B. Porter.	Nov. 23.	Negative.	Negative.	Negative.
No. 12. Carcinoma breast. Periphery of } growth. Dr. Warren.	Nov. 25.	Negative.	Negative.	Negative.

	1899.	CARCINOMA BOUILLON.		PLAIN BOUILLON.		BLOOD SERUM.
		Aërobic.	Anaërobic.	Aërobic.	Anaërobic.	
No. 13. Carcinoma breast. Periphery growth. } Dr. Warren.	Dec. 5.	Negative.
No. 14. Carcinoma breast. Lymphatic gland. } Dr. H. H. A. Beach.	Dec. 8.	Negative.
No. 16. Carcinoma breast. Periphery growth. } Dr. H. H. A. Beach.	Dec. 16.	Negative.
No. 17. Carcinoma nose. (Cocci in cover glass } from blood at operation.) Dr. Warren.	Dec. 21.	Negative.	Staphylococcus Pyogenes Aureus.
Carcinoma breast. Lymphatic gland. Dr. } A. T. Cabot.	Dec. 29.	Negative.
No. 19. Carcinoma breast. Periphery growth. } Dr. H. H. A. Beach.	1900. Jan. 2.	Negative.
No. 20. Carcinoma breast. Periphery growth. } Dr. C. B. Porter.	Jan. 10.	Negative.	Negative.
Carcinoma breast. Lymphatic gland. Dr. } C. B. Porter.	Jan. 15.	Negative.

	1900.	CARCINOMA BOUILLON.		PLAIN BOUILLON.		BLOOD SERUM.	BOUILLON. Mucosa Pig's Intestine.		AGAR. Mucosa Pig's Intestine.	
		Aërobic.	Anaërobic.	Aërobic.	Anaërobic.		Aërobic.	Anaërobic.	Aërobic.	Anaërobic.
Lymphatic gland and surrounding tissue.	Negative.	Negative.	Negative.
	Negative.	Negative.	Negative.
Normal sterile gland inoculated from tumor mass.	Negative.	Negative.
	Negative.	Negative.
Piece of normal breast inoculated from diseased breast.	Negative.	Negative.
	Negative.	Negative.
Piece from breast young woman in- oculated from tumor mass.	Negative.	Negative.
	Negative.	Negative.
Lymph gland. No. 21.	Feb. 15.	Negative.
Tumor mass. No. 21.	Feb. 15.	Negative.
Carcinoma stomach. Peritoneal fluid. Dr. M. H. Richard- son.
	Mar. 17.	Negative.	{ Plain Bouillon and Agar made from a cystic breast. Negative. }		Negative.
Carcinoma breast. Periphery growth. Dr. Harrington.	Negative.
	July 14.	Negative.

All of the above cultures were observed for ten days over longer periods of time and in their examination the condition of the medium was noted, microscopical examination of unstained and stained slides made, and portions of inoculated material in some instances were hardened, cut and stained for microscopical examination.

Contaminations.

In many of the cultures, especially those made in carcinoma bouillon and under anaërobic conditions, no microorganisms were seen. The microscopical examination showed disintegrating cells. In other cases, after a day or two, bacillus and coccus forms occurred similar to those usually found in contaminated cultures. Over long periods of time all cultures became contaminated. In one or two instances sub-cultures, from the original cultures showing microorganisms, were made on plates and tubes under aerobic and anaërobic conditions, but nothing which could be identified with the so-called carcinoma bodies seen in sections of hardened tissue was demonstrated.

Previous to this series of culture experiments, we had made in this laboratory a number of attempts to obtain a characteristic growth from carcinomatous tissue, but they were all negative.

The result of our investigations is, that in the case recorded above we were unable to grow from carcinoma tissue anything which could be regarded as a specific living organism.

SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society; the next will be held on November 20, at the Harvard Medical School, at 8 P.M.

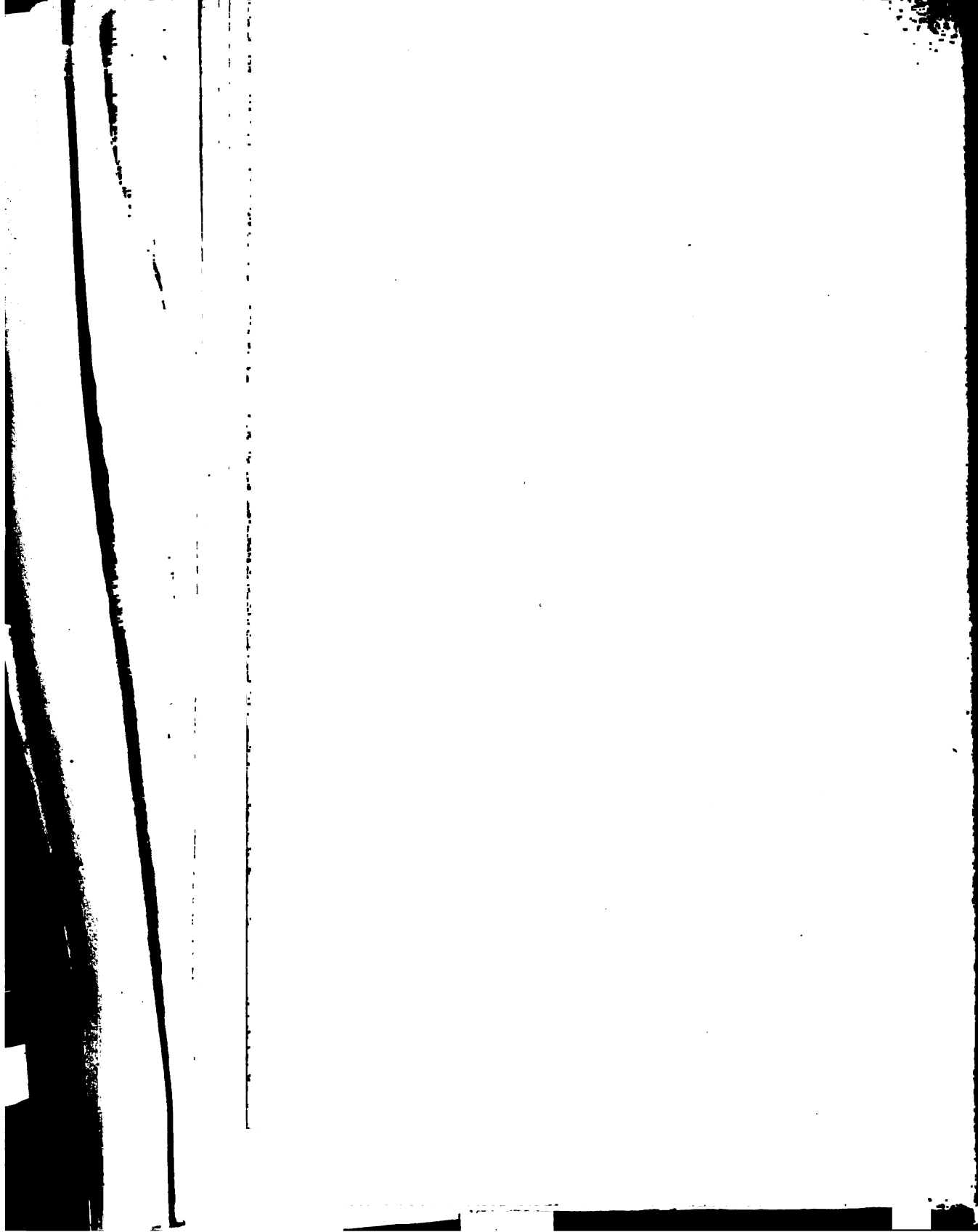
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STUDIES IN MUSCULAR FATIGUE AND SORENESS.

EDMOND HOUGH.

*of the Massachusetts Institute of Technology.)**(Abstract.)*

Experiments were first made by rhythmically contracting and recording the height of contraction. Franz, and the writer have used a constant weight, since the former will always give the same result, no matter how great the weight of the muscle, no matter how great the weight of the muscle. The latter a point is usually reached at which the muscle can no longer lift the weight. The muscle is still capable of lifting a smaller weight, and thus evidently gives an incorrect measure of the capacity of the muscle and of its state of fatigue. A record of a series of rhythmic maximum contractions, in which the resistance of a spring is connected with the muscle, gives a curve of fatigue, which is more correct than is the record obtained with a constant weight.

It should be borne in mind that the use of a spring has certain advantages over that of the constant weight, inasmuch as the muscle normally contracts against constant

while the second and third phalanges are flexed by the *mm. flexores digitorum* in the forearm, the first phalanx is flexed chiefly by the *mm. lumbricales* in the palm of the hand. Maximal extension of the spring must depend in this case on perfect coördination in the working of two very different sets of muscles, thus introducing a third factor over and above those of strength of stimulation and the condition of the muscle as regards fatigue.

A double metal splint was attached to the distal phalanges of the middle finger; flexion was thus possible only at the joint between the first and second phalanges, as already described. The dorsal half of the splint carried an adjustable hook (for the attachment of the finger to the spring) which was made fast at a constant distance (determined by a T square) from the joint, so that the muscle worked with the same leverage in all experiments. The neglect of this mechanical principle is a serious source of error in most ergographic work.

It is very important that more attention be paid to such matters as leverage in ergographic experiments. It has been tacitly assumed that the pull of the flexor on the finger is comparable to the pull of an excised muscle on a weight which it carries. This is, however, by no means the case. In the first place, the attachment of the flexor muscle to the bone introduces a lever system, in virtue of which, as the bone passes from the condition of extreme extension to that of flexion, the pull is applied at increasing mechanical advantage. In the second place, as the finger is flexed, the relative direction of its movement and of the application of the resistance constantly changes, so that, even could the weight be attached directly to the bone at the point of insertion of the muscle, the movement produced in the weight would be a constantly varying component of that produced in the bone. In the third place, the weight is not attached at the point of insertion of the muscle, but by a joint situated between one and two centimeters from this point; consequently, as the finger is flexed, of the total energy applied at this joint the component exerted in the direction of the pull

worthy of close attention unless it has been taken from a subject who has trained himself to neglect these sensations as far as possible, since the constant streaming into consciousness of any painful sensation must seriously interfere with the exertion of maximal efforts of the will. With practice it becomes possible to make ergographic experiments of from twenty to thirty minutes' duration without serious error from this source. It is, however, an open question whether the afferent impulses thus entering the nervous system may not diminish the amount of volitional innervation even when they do not affect consciousness. The worker with this method of studying fatigue must be constantly on his guard to avoid attributing to fatigue what is really due to other causes.

Fatigue of the Trained Muscle.

We shall see later that when an untrained muscle makes a series of maximal contractions against a strong spring, a soreness of the muscle results which cannot be regarded as a phenomenon of pure fatigue. In the trained muscle, on the other hand, these complications are absent, and the course of events is very regular and typical. It is consequently convenient to begin with the fatigue of the thoroughly trained muscle.

The fatigue curve of a series of maximal rhythmic contractions. — We shall indicate the duration of the periods of work and rest by the convenient formula $\frac{C}{R} = \frac{m \text{ sec}}{n \text{ sec}}$, where C represents the period of contraction and R the period of rest before the succeeding contraction.

Ergographic work has usually been done with the rhythm $\frac{C}{R} = \frac{1 \text{ sec}}{1 \text{ sec}}$. In most of my experiments I have used, instead, the rhythm $\frac{C}{R} = \frac{1 \text{ sec}}{2 \text{ sec}}$, the metronome beating half seconds. The latter rhythm is not so monotonous as the former and a trained muscle can reach its maximal contraction in a half second as well as in a second.

The curve in Figure 3 is accurately plotted from one of these tracings. The abscissæ represent time in minutes, while the ordinates represent height of contraction. As a contrac-

STUDIES IN MUSCULA

Figure 4 gives a curve p shows very clearly the effect of fatigue. Upon changing rhythm, the curve gradually from which it gradually falls to the former rhythm. When $\frac{1}{2} \frac{\text{sec}}{\text{sec}}$, or slower, there is no traction in the trained muscle contraction can almost at adopting the slower rhythm

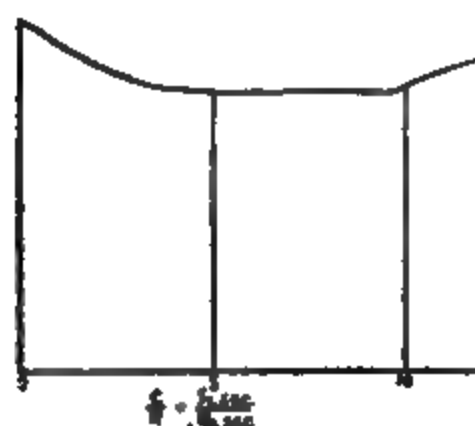


FIG. 4. — Curve of fatigue, plotting showing the effect of fatigue. Figure

expressed with the mathematics these fatigue curves, and accurate indication of the

Turning for the moment fatigue, I think it is evident is what we should expect ordinary fatigue thus far the products of activity; it is that these limit the expenditure) in proportion to the under the conditions of moving them; and it would $\frac{C}{R} = \frac{1 \text{ sec}}{9 \text{ sec}}$ the removal is contracting. As the rhythms are not completely removed

end of the experiment. The fatigue levels of these three tracings are in no respect different from those of controls on other days without smoking. Indeed, in one of them exactly the same level was established in all three tracings, and this was the same before and after lighting the cigar, although the prolonged smoking had exerted a marked physiological effect before the conclusion of the experiment.

Observations upon Muscular Soreness.

In the latter part of November, 1899, the writer began a series of experiments upon the ergograph after a rest of a little over six months. The tracing taken on the first day was without discomfort. On the following day, however, the flexor muscle was quite sore. Tracings were taken on this and the four succeeding days, the muscle remaining very sore during the entire period; a rest of three days was then allowed and another tracing taken. This procedure was repeated during the succeeding three weeks, and the condition of the muscle during the recovery from soreness tested by tracings. When compared with the fatigue curves of the same muscle in training six months before, these curves show the following features:

1. The untrained muscle failed to come to a constant fatigue level, the height of its contractions continuing to diminish to the end of the experiment (20-25 minutes). This was not accompanied by any painful sensation (soreness) either during the tracing or for some hours afterward.

2. Eight or ten hours afterward the muscle began to feel sore, especially when made to contract against resistance. This soreness increased and was at its height about twelve or more hours after taking the tracing.

3. The tracings given by the muscle in this condition were at first very painful; the pain, however, gradually wore away in the course of five or ten minutes, or was noticed only at the height of contraction.

4. Such tracings showed a marked diminution in the height of contraction (against a spring), even when all feel-

Kind of contraction.	Number of subjects.	SORENESS.		
		During work.	3-4 hours after.	12-24 hours after.
$\frac{C}{R} = \frac{\frac{1}{2} \text{ sec.}}{\frac{1}{2} \text{ sec.}} \dots\dots\dots$	6	0	0	5
$\frac{C}{R} = \frac{1 \text{ sec.}}{1 \text{ sec.}} \dots\dots\dots$	9	1	0	3
$\frac{C}{R} = \frac{1 \text{ sec.}}{9 \text{ sec.}} \dots\dots\dots$	10	2	2	7
Tetanus $\dots\dots\dots$	14	10	2	4 (2?)

These results bear out in general what I had suspected from my own experience. While soreness may be caused by any kind of muscular work, either during or after the work it would seem that rhythmic contractions, and especially those in which the slowness of the rhythm excludes fatigue are apt to be followed by a soreness twelve or twenty-four hours later, although at the time of work no pain whatever is felt. Tetanic contractions are not so apt to result in soreness on the following day, although the muscle usually feels sore at the time of work.

The most striking feature of the above table is the clear distinction which it draws between fatigue and soreness. As measured by the ergograph, fatigue is most marked in the tetanic contractions, although but rarely are these contractions succeeded by that marked soreness which comes on the following day. In the rhythm $\frac{C}{R} = \frac{1 \text{ sec.}}{9 \text{ sec.}}$, on the other hand, fatigue is practically absent at the time of the tracing and yet the sorest arms noticed were those which had done this kind of work for fifteen or twenty minutes.

Fatigue, strictly speaking, is a phenomenon which accompanies work and is the change in the working capacity of the living cell. It is quite obvious, on the other hand, that other things may interfere with the doing of external work by a muscle fibre; for example, the rupture of the connective tissue which joins the fibre to the tendon, or injury to the

THE TREATMENT OF THE PROTEIDS OF COW'S MILK.

T. M. ROTCH.

The proteids of milk are not only interesting from a chemical standpoint, but are also of much practical importance.

Until lately the results obtained from both chemical and physiological sources have been so negative and unsatisfactory in the comparison of woman's and cow's proteids that but little clinical use could be made of them.

Thus although for a long time we have known that the chief elements which we have to deal with in the composition of the total proteids in woman's and in cow's milk are caseinogen and lactalbumin, yet the casein resulting from the coagulation of the caseinogen in both milks differed so markedly in its size and consistency, and the cow's coagulum caused so much more gastric disturbance than did the woman's, that it has become a fruitful source of discouragement to those who are endeavoring to solve the problem of substitute infant feeding.

The total proteid of cow's milk is about three or four times as great as in woman's milk, and a great advance was made in the management of the total proteid in cow's milk when by means of exact methods we were enabled to order and obtain for the special infant the special percentage of total proteid indicated by the special conditions of the case. In this way the total proteid percentage in the infant's food could be made to correspond to the various total proteid percentages known to occur in woman's milk.

This advance was all the more marked since in previous years it had proved to be almost impossible to obtain by a home modification the exact proteid percentage which might happen to be desired. This inaccuracy arose chiefly from the necessity of using creams with different fat percentages to obtain a variety of proteid percentages, making a somewhat complex problem, and one which resulted in the infant seldom getting the proteid percentage which the physician supposed he was providing. For this reason clinical investi-

accomplished by prescribing for definite percentages of lactalbumin and caseinogen instead of for a total proteid is that we can now materially reduce the coagulated caseinogen to the same percentage as occurs in woman's milk and yet retain the same high total proteid percentage which we had before.

There are at present, however, only certain combinations of the fat, sugar, lactalbumin, and caseinogen which can be provided. Thus while we can obtain with various creams any per cent. of fat, sugar, and total proteids required, we cannot, when varying percentages of lactalbumin and caseinogen are required, obtain a higher total per cent. of proteids than 1.25, and of this the lactalbumin per cent. cannot be obtained higher than 0.75 and the caseinogen higher than 0.50.

This is owing to the fact that the lactalbumin has to be obtained from whey, in which the lactalbumin is about 1 per cent. We are therefore, by this advance in the accuracy of our percentage prescribing, enabled to feed infants on a very low percentage of caseinogen at a period of life when this is especially indicated, and as they grow older the total proteid percentage can be gradually increased as it naturally would when the power of digesting cow's milk caseinogen is acquired and the necessity for a high percentage of lactalbumin in the total proteid becomes less.

CASE I.

CASE II.

THOMAS.

INJURY OF THE CORD.

nipples. The knee-jerks were absent. Operation was performed and a fracture of the spinous process and laminæ of the second dorsal vertebra was found; the cord appeared normal. The patient died about twenty-four hours later, and about twenty-nine hours after the accident. At the autopsy the arches and spines of the second and third dorsal vertebræ were absent; there was a fracture of the bodies of the fifth, sixth, and seventh cervical vertebræ, with displacement backward of the upper fragment; crush of sixth and seventh cervical segments of the cord, with acute softening and hæmorrhage into its substance. No microscopical examination.

Case III. The patient was found upon a bridge, and no history of the accident could be obtained. There was complete paralysis of all the limbs, respiration was diaphragmatic, priapism was present, and the patient could not speak above a whisper. He died in twenty minutes after entrance. At the autopsy there was found a fracture of the fifth cervical vertebra, with dislocation forward of the upper fragment; crush of the fifth and sixth cervical segments of the cord, with hæmorrhage into its substance, chiefly into the gray matter, extending from the second to the seventh cervical segments; œdema of the cord; diffuse acute degeneration of axis cylinders and myelin sheaths throughout the cord; moderate acute diffuse degeneration of nerve fibres of ventral and dorsal nerve roots; and fracture of the sternum. A microscopical examination was made.

Case IV. The patient fell from the elevated railway structure, striking upon his head, which had caused a scalp wound. There was absolute paralysis of the lower extremities, with absent knee-jerks, and complete loss of sensation as high as the seventh rib. The arms were unaffected. There was a small knuckle at the fifth dorsal spine, there was retention of urine, and respiration was carried on by the diaphragm alone. Death occurred on the third day. At the autopsy there was found a fracture of the fifth cervical and of the fourth, fifth, and sixth dorsal spines, and of the body of the sixth dorsal vertebra, with displacement forward of the upper fragment; crush of the third, fourth, fifth, and

first case, where the microscopical examination of the showed the lesion to be partial. In Cases I. and V. the paralysis of the arms was of the so-called lower-arm type, involving the adductors and abductors, the deltoid, biceps, and triceps, and the loss of sensation came to about the level of the seventh rib on the trunk, and involved the ulnar side of the hand and forearm in one case and the ulnar side of the hand and whole arm in the other. In Case II., where the injury was at nearly the same level, there was no paralysis of the arms noted, and sensation was lost below the nipples only. In Case III. the arms were completely paralyzed; and in Case IV. they were unaffected, and sensation was undisturbed below the seventh rib, as one would expect.

In Case I., where the lesion was a partial one, the knee-jerks were present; in all the other cases they were absent, where noted. In regard to the other reflexes the condition varied. The plantar reflex was absent in Cases II. and IV. and present, though slight, in V. The abdominal reflex was absent in Cases III., IV., and V. The cremasteric reflex was absent in Cases III. and IV., and slight on the right in Case V.

In four cases the breathing is stated to have been carried on by the diaphragm only, and priapism or retention of the urine was noted in every case.

The duration of life varied from twenty minutes after admission (Case III.), the time after the accident being unknown, up to five days.

In two cases (I. and II.) an operation was done. In the first case the surgeons were misled by a fractured dorsal vertebra, while the injury to the cord was produced by the fractured bodies of the sixth and seventh cervical vertebræ. In this case the line of fracture extended from a point anterior and above, downward and posteriorly, an exceedingly unusual direction for the fracture to take, not mentioned by any writer, and shown only in three of Wagner and Stolper's illustrations. In the other operative case the upper border of the field of operation was just about at the point of greatest injury. Thorburn, Kocher, and others call attention to the fact that the injury in these cases is usually higher than one

The treatment of these various forms must vary with the nature of the injury. In some of the partial forms injury of the cord may be absent or slight. In the severer forms the treatment must vary somewhat with the character of the accident. The form of accident may be divided into three classes:

Those producing direct crushes of the arches, whether from a fall, a blow, or a bullet. Thorburn and Wagner and Stolper think these, together with some cases of stab wounds, to be the only ones where early operative interference is demanded. The latter authors limit the late operation to those cases where a late increase of the symptoms can be ascribed to adhesions in the membranes of the cord, arising during the process of healing.

Falls upon the head, buttocks, or feet, producing usually compression fractures.

Forced flexions, or more rarely extensions of the spine, producing dislocations either with or without fractures of the vertebral bodies.

The second class of accidents will seldom produce permanent pressure upon the cord from fragments of bone, because of the strong ligaments lying posterior to the bodies of the vertebrae. The third class of accidents is the one usually producing the complete luxation fractures. In these cases the fracture can usually be removed, and the narrowing of the spinal canal obliterated by hyperextension of the spine, sometimes with, sometimes without extension, and this was shown in our cases, but especially well in the spine from Case 1, of which two photographs are given: one of the spine flexed, and one of the spine held in a position of hyperextension simply, without extension. In all these cases the marked narrowing of the spinal canal could be produced by moderate flexion — a fact which cannot be carried too constantly in mind while examining or handling these cases. Cases of luxation fracture of the spine should then be treated by hyperextension, with moderate extension and rotation of the spine. Unfortunately the injury of the cord is often a complete transverse one, and even complete rup-

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SOME VARIATIONS

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SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society; the next will be held on December 18, at the Harvard Medical School, at 8 P.M.

All communications should be addressed to the Editor,

HAROLD C. ERNST, M.D.,

Harvard Medical School,

688 Boylston Street,

Boston, Massachusetts, U.S.A.

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MAY 18 1901

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NUMBER 4, 1900.

PHOTOMICROGRAPH OF THE BACILLUS
OF SOFT CHANCRE.

BY B. MALLORY, M.D.

In which I shall show was made by Mr. [unclear] demonstrates clearly the micro-organism preparation which I made of the [unclear] the typical case of soft chancre men- [unclear] their morphology, arrangement, and [unclear] seem to be identical with the bacillus [unclear] acknowledged to be the cause of soft

to add to the subject, but will summarize known at present about the micro-

described and described by Ducrey in 1889 of soft chancre. The results which he [unclear] been confirmed by Krefting, Unna, [unclear] others. The short thin bacillus usually [unclear] are often parallel; it measures 1.5 μ in [unclear] thickness, has rounded ends, and usually [unclear] the middle. The bacillus stains readily [unclear] blue solution, but is rather quickly

JOURNAL OF

LORY.

it is, along the surface of the ulcer in the zone of disintegration, they die off.

The bacilli are not found in the buboes, which are due chiefly or entirely to the absorption of toxic

THE ETIOLOGY OF THE CHANCROID.

ABNER POST.

half a century the etiology of the chancroid has been a subject of great interest. The chancroid was separated from the initial chancre by Bassereau and declared to be a special entity, distinct from syphilis. This new doctrine was accepted for many years and gave rise to a division of logographers into two schools, the unicists, who believed that there was at least some relationship between the chancroid, and the dualists, whose names represent their belief in two absolutely

distinct entities. Bumstead read a paper before the International Congress in which he advanced the doctrine that the chancroid is the result of the inoculation of ordinary syphilis. Ducrey read a paper before the International Congress of Dermatology in which he described a bacillus which he believed was the etiological factor in the production of the chancroid.

He published at least two papers on the subject, and it is at this streptobacillus of Ducrey is commonly known that it is the only micro-organism in the chancroid which has not been found elsewhere. He has never failed to find this bacillus in chancroids.

The latest text-books of bacteriology — that of Koch — says:

"The evidence that this organism is the causal agent of the chancroid accordingly rests on the facts, well established, that the organism is apparently always present in the sore and in its tissues; that it has not been found hitherto in no other form of ulceration; and that it is well marked off from saprophytic organisms by its inability to be obtained in cultures outside the human body. Although the bacillus of Ducrey has been acci-

THE ETIOLOGY

the thigh. The ulcerated in the latter case immediately beneath the tissues in areas of the tracts uniting its lines converge and there communit ulcerating opening system of sewerage. The ramifications of the thin, virulent secretion these features together were complication of particularly among filth and among those poverty, hospitalism, and It seems justifiable chancroid are not necessarily seem to be entirely must expect to find the One explanation of authors as to the etiology is that the individual cases, and those who first from the same chancroid of ulcerations, and of differently different varieties entirely different species called chancroid in would be called the lesions which show character noted from Hyde was a good example, and are different bacillus, perhaps It was my fortune diseases which lay side by side the different character were the result of chancroids.

THE ET

ed sore. The o
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In conclusion a
est probable exp
een different aut
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SCIENCES.

VOL. V PLATE XI.

ANAEROBIC BACTERIA.

en run in. For this reason it should be the manipulations above described.

it that there is danger of contaminating from the alkaline pyrogallic acid mixture the sides of the tube. This does not pass of the cotton stopper is sufficiently completely the quantity of fluid in it, with a e.

od has given satisfactory cultures with e tetanus bacillus obtained from cases of sachusetts General Hospital, and with anaërobic bacteria. It can be applied -tube cultures, both in solid and fluid narch roll cultures. Although it has not res in flasks, there seems to be no reason used for this purpose.

g photograph shows the appearance of a ed according to this method.

f those who have not had much experi- vation of anaërobic bacteria, the writer a result of his experience, the following ss essential for the successful cultivation

e, agar agar, or bouillon used as culture 1 one per cent. of glucose, and should be immediately before inoculation.

media should be freshly prepared.

1 should not be more acid to phenol- of the scale of the Bacteriological Com- ican Public Health Association. The media is of great importance, and is prob- ause of failure to obtain the growth of in culture media. These points are to be observed in the case of cultivation per cent. glucose bouillon growth seems t a reaction nearer the neutral point of 1 to the point $+1.5$ above mentioned.

OCCURRENCE OF THE TYPHOID BACILLUS

temperature to the normal. At the time of the blood-cultures and cultures were made from the pus. The blood-cultures were made on blood serum and plain agar slopes. Microscopical examination of the cover glass cultures showed a few pyogenic cocci and a very few rather, short, rod-shaped pyogenic cocci were seen.

The blood-serum cultures showed several gray-white, medium-sized elevated colonies. The agar cultures showed a few discrete colonies on the blood serum.

Microscopical examination of cover glass cultures on the serum and the agar showed end-end irregularly staining bacilli with flagella. No pyogenic cocci were found in the blood-cultures. To determine the classification of the organism, sub-cultures and tests were made:

Caseine slant . . .	{ Gray-white pearly bar irregular edges along No liquefaction of the
Agar agar . . .	{ Gray-white growth a track. No gas produced
Starch . . .	{ No visible change in the
Starch milk . . .	{ Invisible growth. Co medium-sized, rather end, irregularly stain
Starch slant . . .	{ Gray-white, cloudy growth ical examination showed bacilli.
Starch bouillon . . .	{ No indol production.
Starch pepton . . .	
Starch solution . . .	

With a drop of blood from a known case of typhoid fever and ten drops of the bouillon culture from the above, there was prompt loss of motion and clumping of the bacilli, giving a positive Widal's reaction.

The bacilli had many flagellæ and decolorized on heating. From the above evidence we think the organism is the typhoid bacillus in pure culture.

Cultures from the spleen were negative for typhoid bacilli, the cultures from the gall-bladder, liver, kidneys, and the contents of the pelvic abscess yielded a bacillus like the typhoid bacillus and which, on making sub-cultures and tests, — see below, — proved to be that organism.

in serum . . .	{ Moist, shining, confluent growth made up of short, round-ended, irregular staining bacilli.
inatine slant . .	{ Thin, translucent, homogeneous streak with wavy margins.
in potato slant . .	{ No visible growth. Microscopical examination showed plump, round-ended, vacuolated bacilli.
in agar agar stab . . .	{ No gas production.
in milk . . .	No visible change in medium.
in pepton . . .	Turbid. Actively motile bacilli.
inham's peptone solution .	{ No indol.

The bacillus decolorized by Gram and Widal's reaction positive.

Fœtus. Case No. 1.

The patient, a woman, was in the General Hospital, west medical side, service of Dr. Fitz, in October, 1896. She was sick with typhoid fever, and during the disease aborted. The fœtus was sent to the laboratory, where cultures were made. The only growth obtained was in the culture from the liver.

This growth was a moderate sized, round, gray-white, translucent colony. Microscopical examination showed round-ended, irregularly staining bacilli of various sizes and lengths. Sub-cultures and tests were made as follows:

inatine slant . . .	Thin, translucent, non-liquefying streak.
in agar agar stab . .	No gas production.
in potato slant . . .	{ Invisible growth. Microscopical examination showed vacuolated, short and long, round-end bacilli.

The details of the growth in these cultures and the character of the organism found are given in the following table:

Cultures from Fœtus and Placenta on Blood Serum.

Heart	}	Growths appeared in 24 hours as a gray-white scum of small, round, slightly-elevated colonies.
Liver		
Kidney		

Microscopical examination of cover glasses made from the growths, stained with carbol fuchsin, showed rather short bacilli with rounded ends and staining irregularly.

Placenta	}	Similar growths, but in the cover glass there were besides the bacilli, as above, a few long bacilli with rounded ends and staining irregularly.

Microscopical examination of the water of condensation from all the above cultures showed bacilli with considerable motility.

The following cultures and tests were then made to demonstrate as to whether the bacillus was the bacillus of typhoid fever or not. The sub-cultures and tests were made with bacilli from the growth from each organ and run through separately.

OCCURRENCE OF THE TYPHO

nengen and Hinterberger's stains, t
gellæ.

Widal's Reaction

art.	} Plain bouillon, 4 tubes. 24- hour-old cult- ures.	{ 1 drop of mother's l to 10 dro the cultur
er.		
dney.		
centa.)		
		{ With bl from an known ca typhoid.

Report of Dr. Mark W. Richardson

Cultures from placenta, heart, liver,
hoid serum B 8 in a dilution of 1:3
This gives loss of motion and char
e minutes.

A similar reaction takes place in a sin
h known typhoid (hospital) culture
From the above cultures and tests
ism obtained from the foetal and 1
hoid bacillus.

Sections of the foetal tissues were cu
atisfactory. They showed, howev
merous bacilli morphologically c
hoid bacillus.

In the "American Gynæcological an
June, 1900, Dr. Dorland, in an arti
ssion, calls attention under the hea
e following instances of the recovery
m foetal tissues in cases where the
ve typhoid fever.

Reher in 1885 recovered the bacill
een of a six-months' foetus.

Neuhaus in 1886 obtained similar
onths' foetus.

Eberth in 1893 recovered the bacillus from the blood of the heart and other foetal organs.

Janisewski in 1894 obtained the bacillus from the spleen, intestine, mesenteric glands, kidneys, and lungs of a foetus delivered in the eighth month of pregnancy, and who survived for five days. The autopsy showed an enlarged spleen.

Freund and Levy in 1895 recovered the bacillus from the placental blood and from the blood of the heart and spleen of a foetus delivered in the fifth month of pregnancy. The autopsy showed a somewhat enlarged and softened spleen.

Etienne in 1896 recovered the bacillus from the blood of the heart and from the spleen, liver, and placenta. The foetus was discharged during the fifth month of pregnancy, and showed nothing remarkable at autopsy.

Fordyce in 1898 examined a five-months' foetus from a fatal case of typhoid fever, the mother dying shortly after miscarriage. The autopsy of the foetus showed nothing abnormal. From the kidneys, spleen, and intestinal contents the bacillus was recovered. The blood was sterile. Bacilli could be demonstrated in the tissues by microscopic examination.

Fränkel and Kinderlen failed to get the organism in foetal tissues from undoubted cases of maternal typhoid fever. Couvenaint in 1894, and Dorland in 1899, each record a case where the mother had typhoid fever, but the foetus was born alive and showed no signs of the disease.

The above positive cases agree fairly well with ours except that the bacilli were demonstrable in the sections of the foetal tissues of our second case.

OBSERVATIONS ON MILK COAGULATION AND DIGESTION.

FRANKLIN W. WHITE, M.D.

(From the Chemical Laboratory of the Massachusetts General Hospital.)

The proteid element in cow's milk is the portion most likely to cause trouble in infants and other persons whose digestive powers are feeble. Various methods have been used to render it more digestible, such as diluting or peptonizing the milk, or the addition of mucilagenous substances to render the milk curd finer and softer, that it may be more readily broken up and expose a larger surface to the action of the digestive fluids, and also render the passage through the pylorus more easy.

This last method is the one we shall consider, and usually consists in diluting the milk with decoctions of cereals such as oats, barley, rice, or wheat. Our observations have been made to determine

(1.) Whether or not these cereal decoctions render the milk curd more fine and soft than simple dilution with water.

(2.) Whether one cereal is better than another for this purpose.

(3.) Whether or not the property of yielding a fine curd is wholly due to the starch in solution, and if so, what percentage of starch is desirable.

(4.) To test the value of certain modifications of the method which have been recommended.

(5.) To determine the effect of lime water and of albumen upon the casein curd.

The method is an old one, and the clinicians, especially the pediatricians, have always been more interested in the results than the chemists and have written most about it.

Heubner (1), Jacobi (2), Starr (3), and others believe that cereal decoctions mixed with milk have the power of getting between the particles of curd mechanically during coagulation and preventing their running together and forming a large compact mass. Chapin (4), after careful experiments in test tubes and on dogs with a fistula, came to the

WHITE.

believes that the particles of cellulose of the cereals, suspended in the fluid, are subjected to a mechanical action on the coagulum. L. Smith (5) recommends that the curd be digested by the action of diastase, and is more digestible and still preserves its nutritive value. According to Chapin, its action on the curd is similar to that of Rotch and Harrington (6) from their experiments. They conclude that the size of the curd is determined by the amount of dilution of the milk rather than by the nature of the diluent, that barley water is superior to water, and that under the same conditions plain water is the most efficient diluent. Holt (7) and Biedert (8) agree that the same thing more is accomplished by diluting with water.

The value of this method in the feeding of infants is a subject and the difference of opinion as to the best method is a subject for further study. The present study was begun at the suggestion of Dr. J. H. H. H.

Methods. — The coagulation of milk was studied in test tubes, and the results were compared with experiments. In the experiments the conditions which exist in the stomach were simulated; the milk was kept at body temperature and coagulated by rennet or dilute hydrochloric acid. Of the two, the amount of acid required for coagulation was 0.3 per cent., which is the amount found in the stomach of adults. The milk was coagulated by the formation of the curd by invert sugar. The milk was mixed with the diluent and 50 cc. of the mixture was used for the coagulation of casein by rennet. The process from its precipitation was followed by the same observations were made. The temperature 2 or 3 cc. of an active solution of rennet was added to another 1 to 1½ cc. of a 10 per cent.

OBSERVATION

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An analysis of 4 speci
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Starch	.
Fat	.
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This analysis shows t
portance in the soli
ount to have any effe
In our experiments
s $1\frac{1}{2}$ per cent. starch
1 per cent. of starch.

intermediate between the two. The next step was to test these results in the animal stomach. Cats were first used for this purpose, healthy animals which had been kept in confinement for a week or more to accustom them to their surroundings. The cats were fed and remained after feeding in the same room in which they had been kept, to avoid the disturbing influence of fear or excitement during digestion. They received no food for 24 hours before the experiment, to insure the stomach being empty, and then were given 50 or 100 cc. of the milk mixture and one-half hour or one hour later were killed with chloroform, the stomach removed, and its contents examined.

The character of the curds was noted, also the amount of gastric contents, the total acidity, and amount of free HCl in each case. As no perceptible differences had been noted between the various cereals in the preliminary experiments, barley water was used in all the animal experiments.

In Series I. three cats were fed with 50 cc. of a mixture of milk, with an equal part of (*a*) water, (*b*) barley water, (*c*) barley water dextrinized for 20 to 30 minutes with taka diastase. At the end of one half hour the cats were chloroformed and the gastric contents examined.

Series II. was a repetition of the first, using 80 cc. of the above mixtures.

Series III. was a repetition of the first, allowing digestion to go on for one hour before chloroforming the cats.

The milk mixtures were also tested in a dog with a gastric fistula. I am greatly indebted to Dr. M. Vejux-Tyrode for performing a successful operation for fistula upon the dog which was used. The dog was fed with 100 to 200 cc. of the milk mixtures, on an empty stomach; and after one-half or one hour the contents allowed to run out by removing the upper of the fistula tube, and the stomach gently irrigated with a little warm water. One half hour or more was allowed to elapse between successive experiments.

The fistula did not leak, the dog remained in healthy condition and gained weight during the experiments.

In Series IV. the dog was fed with 100 cc. of a mixture

WHITE.

h an equal part of (*a*) water, (*b*) barley water dextrinized for 20 to 30 minutes with t
At the end of half an hour the gastric contents
red.

was a repetition of Series IV., using 200 cc

. was a repetition of Series V., allowing the m
remain in dog's stomach one hour.

ts were as follows:

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ients was more striking, if anything, in the stomach
test tubes. Where water was used the casein w
st part gathered together in one or more so
sses, surrounded by a rather clear whey. Wh
r was used it was in the form of fine soft flak
ributed. Where dextrinized barley water w
rd was much coarser and tougher than with pl
r, and approached closely the curd yielded
water.

npanying photographs were taken of the stomac
two of the cats after it had been poured out in
s dish. One cat had been fed one half-hour p
milk and water, and the other on milk and bar
y show the striking contrast in the size a
of the milk curd.

unt of gastric contents in the cats in Series I. a
rom 30 to 35 cc.; in Series II. from 50 to 55
l was present in any case. The total acidity
l II. was 0.17 per cent. to 0.20 per cent.; in Ser
cent. to 0.14 per cent.

unt of gastric contents in the dog in Series
ed from 50 to 60 cc.; in Series V. from 100 to
idity in Series IV. and VI. was free HCl o
o 0.12 per cent., total acidity 0.20 per cent.
nt.; in Series V. no free HCl, total acidity o
0.21 per cent.

rences in the curds above noted were constant
s of observations and cannot be explained

PLATE XII.

EVOLUTION.

differences in the conditions of the stomachs of the various animals, as we have just seen that they were very closely alike.

The digestion of the casein in Series III. and VI., where the milk remained in the cat's stomachs an hour, was farther advanced in the milk and barley water than in the milk and water, and on continuing the digestion of the gastric contents outside the body in the other series the fine curd obtained by using plain barley water, which exposed so much greater surface to the action of the digestive fluids, was naturally much more rapidly and completely digested.

Pasteurized Milk. — Several of the milk and barley water mixtures were heated to 167° F. for one half hour as is ordinarily done in pasteurizing milk, to determine the effect. It was found that there was little difference between heated and unheated milk, but if anything the action upon the curd was slightly improved by heating the milk and barley water together in this way.

Dextrinized Cereal Water. — Now that we have clearly proved the action of barley water in reducing the size and acidity of the milk curd, we must seek for an explanation of this effect. I believe that it is mainly if not wholly due to the starch which is in solution. Starch in common with colloidal substances possesses the physical property of forming fine emulsions, which is analogous to its action in coming between the particles of casein curd and preventing their uniting into a firm mass. This will explain also the remarkable action of the dextrinized barley water. The starch is rapidly converted under the influence of an active ferment to dextrin and then to crystalline maltose, which probably had no effect on the curd; and the greater the degree of their conversion in any specimen, the less its effect on the casein. This view was confirmed by the following experiment:

A specimen of 300 cc. of barley water was dextrinized with $\frac{1}{2}$ gramme of taka diastase. Samples were removed at the start and at intervals of 15 minutes for an hour, and mixed with an equal amount of milk. The milk was coag-

ould enable us to calculate the most desirable amount of starch in tenths of one per cent., but simply that it would indicate approximately how much should be used.

The milk mixtures with 1.5 per cent. of starch gave a fine succulent curd. Those with 0.7 per cent. starch gave a curd only slightly less fine than the first. Those with 0.3 per cent. gave a much coarser curd than either of the first. It seemed to me from these observations that approximately 0.7 per cent. starch was the best amount for practical purposes. If the starch was reduced below this, we failed to get the desired effect on the casein, and on the other hand an increase of starch even to double this amount did not give much improvement in our results.

This point is especially important in the feeding of infants where it is desirable to get the greatest effect on the curd with the least possible amount of starch.

This desired per cent. is easily obtained by mixing the milk with an equal amount of a diluent containing $1\frac{1}{2}$ per cent. of starch in solution, or one-third its bulk of a solution containing 3 per cent. of starch. In infant feeding this barley water simply replaces an equal amount of water in the modification without in any way disturbing the per cent. of the casein, proteid, or sugar.

The receipt given in the early part of this article, which is now in common use, gives a barley water containing approximately $1\frac{1}{2}$ per cent. of starch.

We may be able now to explain the variety of opinions which have been held about the value of barley water as a diluent of milk. It seems possible that those men who have found it without effect may have used too dilute a preparation, or one with too small a per cent. of starch.

Albumen water. — There are two other points which I wish to speak of briefly, namely, the action of albumen water and lime water upon the casein coagulum. Egg albumen is a colloidal substance, and it seemed logical to expect that it would have an effect upon the curd similar to that of starch solutions. Our object was not to replace the milk proteids to any great extent with egg albumen, but simply to dilute the albumen water and note the result.

v's milk, and that without their presence the coagulation of casein by rennet would not take place. We know also that lime water is commonly added to milk in the feeding of infants in the proportion of 5 or 10 per cent., to overcome the acidity which soon develops, and render it amphoteric or slightly alkaline in imitation of the reaction of human milk. We wished to find out whether the addition of this or a larger amount of alkaline calcium salt had any effect on the character of the casein curd.

To 25 cc. of milk (which was slightly acid in reaction) was added an equal amount of a mixture of water and lime water in varying proportions, so that the milk contained 5, 10, and 20 per cent. of lime water. Rennet was then added, and it was found that those tubes having an alkaline reaction did not coagulate, while the rest yielded a large tough curd like that of milk and water. When the alkaline tubes were rendered very slightly acid with acetic acid, the curd appeared as tough masses. These results are explained by the work of Hammersten (9) and of Arthus and Pages (10), who found that a very slight excess of alkali was sufficient to prevent entirely the action of rennet upon casein.

The fistula dog was fed with 150 cc. of a mixture of equal parts of milk and lime water, and the gastric contents withdrawn one half hour later. The lime water had no other effect than to reduce the total acidity of the stomach contents from an average of 0.23 per cent. to 0.11 per cent; the milk curd was like that obtained with milk and water.

It is therefore evident that the addition of lime water in considerable quantity to milk simply prevents the action of the rennet until the alkali is neutralized by the secretion of HCl in the stomach, but does not affect the character of the curd which is then formed. Probably the only effect of the small amount of lime water usually added to milk in infant feeding is to neutralize some of the lactic acid which may be developed in it.

The practical importance of using cereal decoctions as diluents of milk is so obvious that I shall do no more than mention it. Milk is one of the most important of food-stuffs; it is the exclusive food of infants, the basis of the diet of

WHITE.

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SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society; the next will be held on January 15, at the Harvard Medical School, at 8 P.M.

All communications should be addressed to the Editor,

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Medical Sciences.

No. 5.

R 18, 1900.

A STUDY
OF THE
BACTERIOLOGY AND PATHOLOGY
OF
TWO HUNDRED AND TWENTY FATAL
CASES OF DIPHTHERIA

BY

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purpose by Dr. Henry F. Sears]

INTRODUCTION.

Diphtheria may now be considered as the best known of the infectious diseases. It enjoys the singular preëminence that its study has in a marked degree increased our knowledge of pathological anatomy, of bacteriology, and of therapeutic measures in infectious diseases. In no other disease has the discovery of the cause led to measures of prevention and of cure which have been rewarded by such brilliant success.

The literature of the disease is enormous. Since the first definite description of the disease by Bretonneau, in 1826, there have appeared numerous articles on the pathological anatomy, on the relation of bacteria to the disease, and finally on the nature of the curative substances produced in the disease and the means of their artificial production. It is possible to select from the literature a comparatively small number of articles, each one of which represents an important increase in our knowledge of the disease, and by which the development of our knowledge may be traced, namely: first recognition of the disease, Bretonneau; its recognition clinically as a specific, contagious disease, Trousseau; anatomical investigation of the membrane, and its mode of formation, Virchow, Wagner, Weigert, Cohnheim, Nasiloff, Peters; pathological anatomy of remote lesions, Bizzozzero, Oertel, Boes; discovery of bacilli, their relation to the disease, and study of experimental lesions, Klebs, Loeffler, Roux and Yersin, Frosch, Welch and Flexner, Flexner, Wright; discovery of antitoxin, Behring, Roux; clinical evidence of value of antitoxin, Welch, Ernst, McCollom.

In the following article but little is added to our knowledge of diphtheria. The matter presented is based on the largest number of cases of diphtheria which have been studied in

MATERIAL.

All of the 220 cases on which our work is based have come from the South Department of the Boston City Hospital. This is a hospital of three hundred beds, which is devoted to the infectious diseases of children. It is separate from the main hospital, and except in its general management is a distinct institution. Its patients, nurses, and house-officers do not come in contact with the main hospital. The patients are generally received from the poorer classes and often are brought to the hospital from considerable distances. Quite a number of fatal cases reached the hospital in a moribund condition and died in a few hours. Almost without exception all the cases were treated with antitoxin. The bacteriological diagnosis of diphtheria is thoroughly carried out in the hospital, and in all of the cases which we report the diphtheria bacilli were found. The table gives the age and the duration of the disease. Sex was not considered.

There is considerable uncertainty as to the duration of the disease in these cases. The time was reckoned not from the date of entry into the hospital, but from the onset of the disease as nearly as could be determined from the history. The lack of intelligence in the parents or friends of the children made the time of onset in many cases very uncertain. The ages given can be considered as correct. The oldest cases were two aged sixty-five years each; the two youngest were respectively nineteen days and one month old.

The small square in the upper left hand corner of the table, giving the cases up to ten years of age and up to ten days' duration of disease, includes 113 cases, somewhat over 50 per cent. Sixty-one of the cases were from one to two years old and 40 of these were from one and one-half to two years old. Thirty-seven cases were from two to three years

old. The number of those from four to five years of age was slightly greater than that of those from three to four years of age.

These figures differ somewhat from the following table which Cronmeyer has given of 459 fatal cases:

1-2 years	64
2-3 "	81
3-4 "	61
4-5 "	58
5-6 "	42
6-7 "	26
7-8 "	26
8-9 "	18
9-10 "	12
10-15 "	11
15-20 "	24
20-30 "	8
30-40 "	2

These cases of Cronmeyer from the Kiel Pathological Institute extend from January, 1883, to December, 1887. The diagnosis was not made from bacteriological examination though that probably is without influence in so large a number of cases.

As a rule the autopsies in our cases were made a short while after death and the tissues were in a good state of preservation. All tissues were rejected for histological examination in which there appeared to be any post mortem change. At the autopsy, routine bacteriological examinations were made from the throat, lungs, heart, liver, spleen, kidneys, and lymph nodes, though this was modified in certain cases. While, in the main, the results obtained from these routine examinations can be regarded as correct, there is no doubt that certain organisms often were overlooked but the results certainly are correct as regards the presence of diphtheria bacilli and the common pyogenic organisms.

All the cultures were made on slants of blood serum; the material for culture was obtained by searing the surface

organs and thrusting a stiff platinum spear (previously sterilized) into the tissue. In this way some of the fluid and in some of the parenchyma was removed and rubbed over the surface of the medium. This procedure was of course modified in certain situations.

Small pieces of mucous membrane from the throat, and sections from the lungs, heart, liver, spleen, kidneys, lymph nodes, and bone marrow, were taken at the autopsy and put into a comparatively large amount of Zenker's fluid, which was changed after a few hours. The tissue remained in this fluid for 24 hours. The tissues were then thoroughly washed in water and hardened in alcohol of increasing strength. Alcohol and corrosive sublimate were used to a certain extent for fixation. Various ones of the organs mentioned were frequently omitted from the examination, and in other cases the examination was more extensive, embracing every organ of the body. A sufficient number of organs in cases representing every age and duration of the disease were examined to make sure that no lesions were overlooked. After the tissue was hardened it was cut in paraffin, and the sections stained in various ways. The most satisfactory stains were eosin and alkaline methylene blue, hæmatoxylin and eosin, and the chloride of iron hæmatoxylin and triple (connective tissue) stains recently described by Mallory. In many cases serial sections of the tissues were studied. This is particularly to be recommended in the examination of the lung and kidney. Only in this way can both the character and the topography of the lesions in these organs be accurately ascertained. The anatomical description of the lesions in each organ was written on cards, and from these with the assistance of photomicrographs the lesions in the organ were described. In both lungs and kidneys we have derived great assistance from the photomicrographs of serial sections. By making the prints and following the same places through we were able to obtain some idea of the usually neglected third dimension.

sease are to those in diphtheria. There were also a number of mixed infections with whooping cough, but these have not been put down in the table. The clinical diagnosis of these mixed infections has been taken in all cases, as there

on which an anatomical diagnosis can be bacteriology of these mixed infections has been no other place. There is a greater number of infections among our cases than has been elsewhere writers. Cronmeyer in his analysis of 4 cases in which diphtheria was secondary and 7 in which it was secondary to measles.

Association with tuberculosis.—The frequency with which tuberculosis has been found in connection with diphtheria has attracted the attention of several writers. There

is to be any relation between the diseases; the frequency with which tuberculosis is found in autopsies of children is only an index of the frequency of tuberculosis at the time.

How frequent this disease is is shown by the statistics of Heller in Munich, who found tuberculosis in 41.8 per cent of autopsies on children. Berliner found 19 cases

in 107 autopsies on diphtheria in Freiburg, or 17.8 per cent, certainly a wide difference from the statistics of Heller in Munich. The tuberculous lesions were usually

found where they were not influenced by diphtheria. In rare cases, according to Berliner, an eruption of miliary tubercles was produced by diphtheria, being possibly due to a chemical change in the blood increasing susceptibility. Cohausen

in his analysis of 459 cases of diphtheria in Kiel found 95 cases of tuberculosis. He gives the following table of

	Per cent.
Infants, 1-2 years . . .	23.0
2-3 " . . .	17.9
3-4 " . . .	13.6
4-5 " . . .	12.6
5-6 " . . .	8.4
6-8 " . . .	8.4
8-10 " . . .	5.2
10-12 " . . .	5.2

	Per cent.
1 case, 12-14 years . . .	1.05
1 " 14-16 " . . .	1.05
1 " 16-20 " . . .	1.05
1 " 20-30 " . . .	1.05
1 " 30-50 " . . .	1.05

Nearly one-half of the cases of tuberculosis could be regarded as definitely healed. In one-third of the cases there was a fresh outbreak of tuberculosis which he attributed to the influence of the diphtheria.

The statistics of Müller show so much larger a percentage of tuberculosis than has been found in the autopsies on cases of diphtheria that it is difficult to explain them.

In nearly all of our cases there were no clinical evidences of tuberculosis and the character of the lesions was not such as would have given rise to symptoms.

Cronmeyer found in 459 cases of diphtheria 60 cases of various forms of tuberculosis, or 13.3 per cent. He thinks that diphtheria both favors new infection with tuberculosis, and fresh extension of old tuberculous lesions, a view which is not favored by the small percentage of cases which he found.

Tuberculosis was found in 35 of our 220 cases, or in 16 per cent. In 3 cases miliary tubercles were found on microscopic examination only. In one case there was tuberculosis of lungs, liver, spleen, œsophagus, intestine, epiglottis, larynx, mesenteric, bronchial, cervical, mediastinal, and axillary lymph nodes, middle ear, temporal bone, and elbow joint. This was in a child one year old, who died two days after entry into the hospital with laryngeal diphtheria. In three cases the lung, liver, spleen, kidney, and mesenteric and bronchial lymph nodes were involved; in one of these cases the cervical lymph nodes, pleura, and pericardium also were involved, and in another there was tuberculous meningitis with a solitary tubercle of the cerebrum. In 3 cases there was healed tuberculosis of the lungs without lesions elsewhere. Of the other cases the lung alone was involved in two; lung

with bronchial lymph nodes in two; lung with bronchial lymph nodes and intestine in two; lung with bronchial and mesenteric lymph nodes in two; lung with bronchial and cervical lymph nodes in two; lung with liver in one, lung and mesenteric lymph nodes in one; liver alone involved in one; liver with intestine, and mesenteric and cervical lymph nodes in one; liver with intestine and mesenteric lymph nodes in one; spleen with mesenteric lymph nodes in one; mesenteric lymph nodes alone in seven; mesenteric and cervical lymph nodes in one; mesenteric lymph nodes and intestine in one; bronchial lymph nodes alone in one; cervical lymph nodes alone in one.

It is shown by this analysis that tuberculosis was most frequent in the mesenteric lymph nodes, which were more frequently involved than either the lungs or the bronchial lymph nodes. In 7 cases the mesenteric lymph nodes were affected without tuberculosis elsewhere. In only 6 of the 18 cases of tuberculosis of these lymph nodes was there intestinal tuberculosis. Cronmeyer in his cases found the mesenteric lymph nodes more frequently the only seat of tuberculosis than any other organ in the body; all of these statistics point to the frequency of infection by way of the alimentary canal. The two youngest of these cases were respectively three, and four and one-half months old. In the case three months old the tuberculosis was limited to scattered miliary tubercles in the lungs and liver, and in the four and one-half months' case there was extensive general miliary tuberculosis¹.

In addition to these more common mixed infections the following unusual cases occurred:

1. *Diphtheria after pregnancy*. — March 18, labor took place outside the hospital; manual dilatation and forceps were employed. March 25, patient entered hospital with puerperal septicæmia and with membrane on throat. Diphtheria bacilli found in cultures from throat. Death April

¹ We think that the frequency of tuberculosis in young children without any clinical evidence of its presence is generally underestimated. The rapidly fatal cases of tuberculosis which so frequently follow measles and other infectious diseases are due generally to infection, but to the extension of an infection which already

9th. Autopsy: Septic endometritis, thrombosis of veins of pelvis and of inferior vena cava, bronchopneumonia. Streptococci in thrombi.

2. *Diphtheria with erysipelas*. — Child five years old, entered with diphtheria. Erysipelas of forehead, scalp, and cheek on fifteenth day. Died on twenty-second day. General blood infection with streptococcus.

3. *Diphtheria in the course of epidemic cerebro-spinal meningitis*. — Child aged six. On the twentieth day of the meningitis developed membrane on pharynx, palate, and uvula. Cultures showed diphtheria bacilli. Died on twenty-third day with acute glomerulo-nephritis and bronchopneumonia.

4. *Diphtheria with typhoid fever*. — Diphtheria not recognized clinically. The autopsy disclosed the following lesions: Bed-sores. Left tonsil swollen, covered with pseudo-membranous exudation; irregular erosion of post-pharyngeal wall. Membrane covering larynx and epiglottis; trachea injected, no membrane. Both lobes of left lung oedematous, congested, with numerous sharply-circumscribed foci of solidification about bronchi. Slight fibrinous exudate over pleura of lower lobe. A few foci of solidification in lower lobe of right lung. Slight fibrinous peritonitis. Spleen enlarged, weight 300 gms., area of necrosis just beneath capsule; over this the exudate is most abundant. One cm. from this necrotic area is an area of suppuration 2 cm. in diameter. Numerous typhoid ulcers in lower portion of ileum. Mesenteric lymph nodes large.

Cultures from the larynx and lungs showed diphtheria bacilli and streptococci. The spleen contains the typhoid bacillus. (This case is not included in the 220.)

5.¹ *Diphtheria with typhoid fever*. — The intestine showed the characteristic lesions of typhoid fever. There was a purulent infiltration of the sub-maxillary and parotid glands, together with a softened thrombus of the external jugular vein, and embolic foci of suppuration in the lungs. Cultures from the purulent infiltration in the neck and from the lungs showed the diphtheria bacillus and the staphylococcus aureus. Microscopical examination of the thrombus showed large numbers of bacilli morphologically identical with diphtheria bacilli, and a few cocci. The abscesses in the lungs had developed around small branches of the pulmonary artery and contained, in large numbers, the same bacilli as the thrombus. There were also in the small branches of the pulmonary arteries emboli composed entirely of these bacilli. It is to be regretted that the thrombus was saved for histological examination and no cultures made from it. The case is an important one in showing an unusual mode of action of the diphtheria bacillus. (This case is not included in the 220 cases.)

6.² *Diphtheria, tuberculosis, amœbæ coli*. — Child aged three,

¹ Previously reported (Councilman, Journal Boston Soc. of Med. Sciences, Vol. 1).

² Previously reported (Strong, Boston City Hospital Med. and Surg. Reports, 1899).

admitted with laryngeal diphtheria. Was intubed without relief and died on the following day. Autopsy. Characteristic membrane on tonsils, larynx, and trachea. Tuberculous ulcers of ileum, and caseation of mesenteric lymph nodes. Microscopical examination of ulcers showed numerous amœbæ among the cells at the bases of the ulcers.

The following cases as well as case 5 show an action of the diphtheria bacillus very different from that ordinarily found, and bring the bacillus into close alliance with the pyogenic organisms.

7.¹ Jan. 27, 1896, autopsy made on case of diphtheria by Dr. Leary. He was not conscious at the time of any prick or injury of the hand.

February 1 a slight swelling and tenderness around a hair follicle of the middle finger of the left hand. The tissue about the follicle was reddened and slightly swollen. Two days after this a small pin-point pustule developed about the hair. A culture made at this time showed a pure growth of the diphtheria bacillus. The bacilli in culture appeared to be rather larger than the ordinary bacilli, the ends more swollen, and atypical forms were more common than usual. A cover-slip preparation of the contents of the pustule showed cells with a few diphtheria bacilli in them. The finger on February 5 was reddened, a little brawny, scarcely swollen at all. There was nothing in the course of this infection which differed from that of the ordinary pyogenic infections.

Guinea-pig inoculated from the pustule on February 5 died February 7, with the lesions of experimental diphtheria, a great deal of œdema around the seat of inoculation extending down to the belly wall, a fibrino-purulent exudation immediately around the point of inoculation, and on microscopic examination numerous diphtheria bacilli in the pus cells.

8. L. P., employee in the pathological laboratory of the Boston City Hospital, developed a small abscess of the right index finger on the palmar surface. The abscess was opened and the wound healed in a few days. The diphtheria bacillus and the pneumococcus were obtained in the cultures. No inoculation test made

¹ Previously reported (Leary, Boston City Hospital Med. and Surg. Reports, 1896).

BACTERIOLOGY.

The 220 cases¹ studied in this report may be divided according to the clinical diagnosis into groups, thus:

Group I., 161 cases, diphtheria only.

Group II., 59 cases (diphtheria complicated by scarlet fever 34, by measles 16, or by both 9).

These will be spoken of as Groups I. and II. respectively, and will be taken up in the order mentioned. The bacteriology of the general infections will be considered first, and then that of the various organs and tissues. Each of these divisions will be preceded by a brief review of the literature on the bacteriology of the organ considered.

GENERAL INFECTION.

Frosch was the first observer to note in a series of cases of diphtheria the occurrence of the diphtheria bacillus in the internal organs (heart's blood, liver, spleen, kidney, and lymph nodes). In 1895 he reported that he had found the organism in 10 out of 15 cases which he had examined. Kolisko and Paltauf previously, however, had noted its occurrence in the spleen in 1 case, as had also Schmorl in the cervical lymph nodes in 7 out of 10 cases. Booker in 1 case found the bacillus with the streptococcus in the spleen, lung, submaxillary gland, and heart's blood. Kutscher found it in 1 case in the liver and kidney, and in 8 out of 9 cases in the lung.

Canon found it repeatedly in his post-mortem examination. Kanthack and Stevens found it in the lung in each of 26 cases; in the spleen in 10 out of 21 cases; in the kidney in 2 out of 3 cases. Wright in 14 cases demon-

¹ One hundred and fifty-seven cases have been previously reported (Pearce, *The General Infections and Complications of Diphtheria and Scarlet Fever*, Med. and Surg. Reports of the Boston City Hospital, 9th series, 1898; also *Journal of the Boston Soc. of Med. Sciences*, March, 1898).

ated it in the lung 13 times; in the liver 3 times; in the spleen twice; in the cervical and bronchial lymph nodes 5 times; in the mesenteric lymph nodes twice; in the heart's blood once; and in the kidney once. In 7 of these cases there was also a general streptococcus infection. Wright and Stokes in a later series of cases reported 31 cases in which the diphtheria bacillus was found in the lung 30 times; in the liver 9 times; in the mesenteric lymph nodes 7 times; in the spleen and heart's blood each 5 times; in the cervical lymph nodes 4 times; in the brain and bronchial lymph nodes each twice. The streptococcus was present in 20 cases, and the pneumococcus or the staphylococcus pyogenes aureus in 5 cases. Stokes, in 9 cases treated by antitoxin, found it in the lung 9 times; in the kidney 4 times; in the heart's blood and spleen, each once. Nowak in 22 fatal cases found the streptococcus in the internal organs in 21. In 9 of these cases it was associated with the diphtheria bacillus, and in one with a bacillus resembling it except in virulence. Petersen in the examination of 25 cases of septic diphtheria did not always find the streptococcus in the blood or internal organs, and thinks that the diphtheria bacillus alone can produce the so-called septic symptoms. Reiche in examining 42 fatal cases found streptococci and staphylococci in 13 per cent.; streptococci alone in 45.2 per cent.; and the diphtheria bacillus alone twice. Stephens and Parfitt report 3 fatal cases, one with a general infection with the streptococcus and the diphtheria bacillus; the second with the diphtheria bacillus alone; and the third with the diplococcus *puccinellus*. In the second case the bacilli were demonstrated in cultures from the blood during life. Flexner and Babes have each in 1 case demonstrated a general infection with the diphtheria bacillus. Dahmer states that he has found the streptococcus in the blood of diphtheria patients in about 10 per cent. of the cases which he has examined. Out of 100 cases he found it in the heart's blood and spleen in 17; in the lung in 30. In 10 of the latter it was associated with staphylococci. He kept no record of the occurrence of the diphtheria bacillus. Mya found the diphtheria bacillus in

the spleen in 2 cases. Infection with the streptococcus and pneumococcus he found, however, to be more common.

In inoculation experiments with guinea-pigs Wright found the diphtheria bacillus 19 times in 155 livers, 15 times in 152 spleens, 4 times in 151 kidneys, and 7 times in the blood of 153 hearts. Abbot and Ghriskey found that by inoculating the testes of rabbits with diphtheria bacilli, small bodies made up of leucocytes and diphtheria bacilli were found in the omentum. Zarniko in a few cases found diphtheria bacilli in the necrotic foci in the liver in animals inoculated with that micro-organism.

Group I. — In this group cultures were taken in all except 8 cases from the heart's blood, liver, spleen, and kidney. The results are as follows:

Heart's blood; the diphtheria bacillus was found 7 times; 3 times alone; twice with the streptococcus; and twice with the staphylococcus pyogenes aureus: the streptococcus alone 22 times; with the pneumococcus once: the pneumococcus alone once: the staphylococcus pyogenes aureus alone 3 times.

Liver; the diphtheria bacillus 30 times; alone 16 times, with the streptococcus 14 times: the streptococcus alone 24 times: the staphylococcus pyogenes aureus alone twice; with the pneumococcus twice: the pneumococcus and the staphylococcus pyogenes aureus alone each 2 times.

Spleen; the diphtheria bacillus in with the streptococcus 3 times: the times; with the staphylococcus pyogenes pneumococcus in pure culture 3 times: the staphylococcus pyogenes aureus 3 times.

Kidney; the diphtheria bacillus alone 17 times; with the streptococcus 8 times; with the staphylococcus pyogenes aureus twice: the streptococcus alone 27 times: the staphylococcus pyogenes aureus twice; with the pneumococcus once: the diplococcus lanceolatus 7 times: and the staphylococcus pyogenes aureus in pure culture 7 times.

Group II. — Cultures were made in all but 1 case from the heart's blood; the diphtheria bacillus al

the streptococcus 4 times: the streptococcus alone 11 times; with the diplococcus lanceolatus once: the staphylococcus pyogenes aureus alone twice.

Liver; the diphtheria bacillus alone 5 times; with the streptococcus 7 times: streptococcus alone 15 times; with the staphylococcus pyogenes aureus 3 times.

Spleen; the diphtheria bacillus alone 5 times; with the streptococcus twice: the streptococcus alone 17 times; with the staphylococcus pyogenes aureus once; the latter alone once.

Kidney; the diphtheria alone 7 times; with the streptococcus 5 times: streptococcus alone 13 times; with the staphylococcus pyogenes aureus 3 times: the latter microorganism alone 3 times; and with the pneumococcus once: the pneumococcus alone once.

In taking cultures from these organs the amount of material used to inoculate the culture medium (Loeffler's blood serum prepared by the Councilman and Mallory method) was that which would adhere to the sides of a sterilized flattened platinum needle thrust into the organ after its surface had been burned. In the case of the heart's blood the needle was thrust into the right auricle after burning the surface and before the large vessels were cut, or into the blood which escaped on cutting the inferior vena-cava. Thus it will be seen that a comparatively small amount of material was used for inoculation. In most cases, nevertheless, the growth of the diphtheria bacillus was fairly abundant, generally from 5 to 15 colonies on each tube, but sometimes many more. Cultures from the liver sometimes showed as many as 25 to 35 colonies. The spleen cultures never showed more than 10 colonies. The kidney cultures in 2 cases showed 19 and 4 colonies respectively. In some cases the growth was only in the water of condensation. This was especially true in cultures from the heart's blood, in which in only 2 cases were there distinct colonies on the surface of the serum. We agree with Kanthack and Stephens, and Flexner that the bacilli can be found when only the usual amount of material for the culture is used. Most observers consider it necessary

to use a large amount of material in order to demonstrate the presence of the bacillus at all. In some of the cultures from these organs involution or degenerate forms were present in considerable numbers.

The clinical significance of this general infection with the diphtheria bacillus is not apparent. It occurred generally but not always in the gravest cases or in those known as septic cases. In this series of fatal cases the number of infections with the streptococcus was but slightly greater than that with the diphtheria bacillus.

Whether the diphtheria bacillus does or does not continue to produce the toxic products wherever it may be in the blood or internal organs it is impossible to say, but from the number of fatal cases with such an infection it would seem very probable that it does. Kanthack and Stephens incline to this opinion, and as previously stated, Genersisch believes many of the so-called septic cases to be due to such an infection, independently of the streptococcus.

In comparing Groups I. and II. the general infection with the diphtheria bacillus appears to be about equal; thus Group II. with 59 cases has about the same percentage of cases in which this bacillus was found as Group I. with 161 cases. General infection with the streptococcus, however, is comparatively more frequent in Group II. This is not surprising, for the streptococcus is the micro-organism most commonly found in a general infection in scarlet fever. Pearce¹ in a recent study of 21 cases of scarlet fever found the streptococcus in 9 out of 11 cases having a general infection.

PERICARDIUM.

Acute sero-fibrinous pericarditis occurred twice in each group. The streptococcus was found in all 4 cases, but associated with the pneumococcus in 1 case of Group II.

In Group I. occurred 1 case of acute purulent pericarditis also due to the streptococcus.

¹ Pearce, R. M. *Scarlet Fever: Its Bacteriology, and Gross and Minute Anatomy*, Med. and Surg. Reports Boston City Hospital, 10th series, 1899. Also Jour. Boston Soc. of Med. Sciences, Vol. 3, p. 161.

ENDOCARDIUM.

Acute ulcerative endocarditis. — Group I., 2 cases.
Group II., 5 cases.

But 2 cases of endocarditis in which the bacillus of diphtheria has been found in the vegetations are on record. The first was that of Howard, who cultivated from the valvular vegetations in the heart and from infarcts in the spleen and kidney a bacillus identical with the diphtheria bacillus in everything except virulence. Wright reports a case in which the aortic and tricuspid valves were affected and in which cultures showed the diplococcus lanceolatus, the staphylococcus, and a bacillus corresponding to the diphtheria bacillus except that it was non-pathogenic for guinea-pigs.

In one case of the Group I. the streptococcus was obtained in pure culture; in this case there existed a general streptococcus infection. In the other case cultures were sterile.

In a case of Group II., on the mitral curtain was a reddish-grey, soft, clot-like mass firmly adherent to the free edge of the valve. Cultures from this mass showed a pure growth of the diphtheria bacillus. Sections of the vegetation showed fibrin with pus and coagulated material, and here and there single bacilli which resembled those of diphtheria, but no clumps of bacilli. There were also a few cocci in indefinite arrangement. This was a case of scarlet fever with diphtheritic rhinitis, tonsillitis, and laryngitis, with bronchopneumonia of both lungs, and marked general lymphatic hyperæmia. The diphtheria bacillus was also present in the heart's blood, liver, spleen, and kidney. In a second case of this group cultures were sterile and in the other three none were taken.

LUNG.

Thaon (1885) appears to have been the first investigator to study the relation of the diphtheria bacillus to the bronchopneumonia of diphtheria. He demonstrated in histological preparations the relation of the bacilli to the inflammatory process. Various cocci were usually associated with the diphtheria bacillus.

In this same year Darier also reported the diphtheria bacillus associated with the streptococcus in 1 case. In 3 other cases which he reported at the same time the streptococcus was present in pure culture in 1, and with the staphylococcus aureus and albus in 2.

The presence of diphtheria bacilli in this complication of diphtheria has been reported by many observers, some of whom consider it to have an etiological relation, while others believe the associated cocci to be of more importance. It is of interest in this connection that Loeffler in his study of the bacteriology of diphtheria (1884) reports the presence of the diphtheria bacillus in the lung, but explains it as a post-mortem invasion.

In the earlier reports the diphtheria bacillus was not found very often and seldom in pure culture. Thus Strelitz (1891) found it in 1 out of 8 cases. In the others the streptococcus, the pneumococcus, and various staphylococci were found. Flexner (1893) found the pneumococcus in 2 cases, in 1 of which it was associated with the diphtheria bacillus. Its presence was confirmed histologically. In 3 cases Mosny (1891) found the streptococcus, associated in 1 with the diphtheria bacillus. The latter organism has also been reported by Johnson (1891) and Booker (1893) in single cases; by Kutscher (1894) in 8 out of 9 cases, sometimes alone, but generally with the streptococcus or staphylococci; and by Frosch (1893), who found it more frequently in bronchopneumonic foci than elsewhere in the internal organs. All his cases appear to have been mixed infections.

Netter (1892) in 7 cases found the streptococcus in all, and the diphtheria bacillus in 4. Mya has found the diphtheria bacillus twice in the lung, but considers the streptococcus and pneumococcus to be the micro-organisms more frequently present.

Horton-Smith (1897) in 2 cases found bacillus, associated with the pneumococcus coccus in one, and with the former only in the

Among those investigators who have found the diphtheria bacillus in a large number of cases are the following:

Wright and Stokes (1895), who found it in 18 of 19 cases, 8 of which it was in pure culture, in 5 associated with the streptococcus, and in the others with various combinations of the pyogenic cocci and the pneumococci. The streptococcus occurred alone in 1 case. They believe that the diphtheria bacillus can cause a bronchopneumonia.

They also found the diphtheria bacillus in the lung in 12 cases in which no bronchopneumonia was present. Belfanti reports 26 cases, in 21 of which he found the diphtheria bacillus; in 4 it was in pure culture. The streptococcus occurred in 20 cases, the staphylococcus aureus in 10, the pneumococcus in 3. He concludes that the diphtheria bacillus either alone or associated with the other microorganisms may cause bronchopneumonia.

Kanthack and Stephens (1897) found the diphtheria bacillus in the lung in 26 cases, in 15 of which bronchopneumonia was present. Various cocci were also present; but they believe the bronchopneumonia of diphtheria to be not of pyococcal origin but a true diphtheritic process.

On the other hand, some investigators have found the diphtheria bacillus seldom or never present.

Sims Woodhead (1895) in 50 post-mortem examinations found it in the lung in only 5 cases. Northrup and Prudden (1889) in an analysis of 17 cases found the streptococcus in 11 (in pure culture in 4), the staphylococcus aureus in 13, the diphtheria bacillus in none.

Woolstein in 14 cases of bronchopneumonia secondary to diphtheria, scarlet fever, and measles found the pneumococcus in 11. In 2 it occurred in pure culture; in the others it was associated with the pyogenic cocci.

In our 220 cases bronchopneumonia was recognized macroscopically in 131. Ninety-eight of these were in cases

¹ A portion of these cases have been previously reported.

Pearce. The General Infections and Complication of Diphtheria and Scarlet Fever. A bacteriological study of 157 cases.) Journal Boston Soc. Med. Sci., March, 1898.

Pearce. The Bacteriology of Lobar and Lobular Pneumonia. Boston Med. and Surg. Journal, Dec. 21, 1897.

of diphtheria only (Group I.); and 33 were in cases of diphtheria complicated by scarlet fever, or measles, or by both.

Group I., 98 cases. No cultures taken in 10 cases, cultures sterile in 6. Of the remaining 82 cases the bacillus of diphtheria was present in 49; the streptococcus in 51; the staphylococcus pyogenes aureus occurred in 27 cases; and the pneumococcus in 10. The diphtheria bacillus occurred alone in 15 cases; with the streptococcus in 17; with the streptococcus and the staphylococcus aureus in 5; with the latter alone in 6; with the pneumococcus in 4; and in the other cases with various combinations of the above. The streptococcus was found alone 15 times; with the staphylococcus aureus 11 times; and with the diplococcus lanceolatus twice. This last micro-organism occurred alone once; the staphylococcus aureus occurred alone 3 times.

In the 10 cases in which no cultures were made sections were stained and examined for micro-organisms. The following results based on morphological characteristics were obtained: In 3 cases the streptococcus was found; in 2 the diphtheria bacillus; in 1 the diphtheria bacillus and the pneumococcus.

In 17 cases of Group I., cultures were taken from the lung, although no inflammatory process was present. In 7 cases with œdema and congestion, the diphtheria bacillus was found alone in 3, and with the streptococcus in 2; the pneumococcus alone once, and with the streptococcus once; the streptococcus with the staphylococcus aureus once, and with the staphylococcus albus once; the streptococcus and the staphylococcus aureus each alone once.

In 3 cases in which small bronchi contained diphtheritic membrane without evidence of bronchopneumonia, cultures contained the diphtheria bacillus. In 2 of these cases the streptococcus was also present, and in 1 the staphylococcus aureus. In a lung with slight diffuse hæmorrhage, the diphtheria bacillus was found; in 1 with tuberculosis the pneumococcus; and in 2 with infarcts the staphylococcus aureus.

Group II., 33 cases. The cultures were sterile in 2, and not taken in 9 cases. In the remaining 22 cases the diphtheria bacillus was present in 20, the streptococcus in 16, the staphylococcus aureus in 10. The diphtheria bacillus occurred alone twice, with the streptococcus 9 times, with the staphylococcus aureus 4 times, and with both 5 times. The streptococcus occurred alone once, and with the staphylococcus aureus once. In 2 of the 4 cases in which cultures were not taken, the pneumococcus and the streptococcus were found each in one case upon histological examination.

In this group cultures were taken in 5 cases from lungs showing only œdema and congestion. The diphtheria bacillus was found in 3 cases, associated in 2 with the staphylococcus aureus, and in 1 with the streptococcus. In the other 2 cases only the streptococcus was found. In the sixth case with organizing pneumonia, the pneumococcus and the bacillus pyocyaneus were found.

No marked difference is seen between the results in Group I. and Group II. The various organisms occur with about the same frequency. The observation of several investigators that bronchopneumonia is generally due to a combination of bacteria is supported by the results in both groups.

Abscesses of the lung. — These were small, often multiple, and occurred in 7 cases of Group I., and in 4 cases of Group II.

In Group I. the diphtheria bacillus was found 3 times; twice with the streptococcus, and once with the staphylococcus aureus. In the other 4 cases the streptococcus and the staphylococcus aureus each occurred alone in one case, and combined in 2 cases.

In Group II. the streptococcus was found alone in 3 cases, and associated with the diphtheria bacillus in one.

PLEURAL CAVITIES.

Empyema. — Group I., 5 cases. The staphylococcus pyogenes aureus was present in one; the streptococcus alone in 2; and associated with the diphtheria bacillus and the staphylococcus aureus each in one. The cause of the

empyæma in this last case was the rupture of a small abscess near the surface of the lung into the pleural cavity. In cultures from other abscesses in the lung the same micro-organisms were obtained.

Group II., 2 cases. In both the streptococcus was present; in one in pure culture, in the other associated with the diphtheria bacillus. In this second case, which had been operated upon, there was a ruptured abscess cavity on the surface of the lung.

The only reference to the occurrence of the diphtheria bacillus in inflammatory conditions of the pleura is that of Frosch, who found it not only in a pleural but also in a pericardial exudate.

Sero-fibrinous pleurisy. — Group I., 18 cases. Unfortunately cultures were taken in only 6 cases. In these the streptococcus occurred alone in 3 cases, the diplococcus lanceolatus alone in 1, the staphylococcus aureus alone in 1, and with the streptococcus in 1 case.

Group II., 5 cases. In 3 cases the streptococcus was present, twice in pure culture and once with the diplococcus lanceolatus. In 1 case the latter micro-organism alone was present.

MEDIASTINUM.

Acute suppurative mediastinitis occurred in 2 cases of Group II. It was due in one case (diphtheria with measles) to the ulceration and perforation of the larynx as the result of intubation. The area of suppuration was most marked from the third to the sixth costal cartilages. There was a rupture of the sternum at the articulation of the fourth costal cartilage, and the fourth and fifth cartilages were free. Streptococci were found in cultures from the pus; on both sides there was a streptococcus pleuritis.

In the second case (diphtheria with scarlet fever) it was associated with acute bronchopneumonia and sero-fibrinous pleuritis and pericarditis. The streptococcus was found in all these exudates, and there was also a general infection with the same micro-organism.

PERITONEUM.

Acute peritonitis occurred in one case of each group. Both were due to the streptococcus. One was associated with the abscess of the spleen mentioned below. In this case there was a general streptococcus infection, abscess of a cervical lymph node, and suppuration of both middle ears.

ACCESSORY SINUSES OF NOSE.

Until within a few years direct extension of an inflammation due to caries of the teeth, with or without necrosis of the maxilla, was considered the most common cause of inflammation of the antra.

It is now known that inflammatory conditions of the nasal mucous membrane, such as coryza, acute and chronic rhinitis, or of the throat, such as tonsillitis or pharyngitis, may involve the antra by direct extension. It is also known that secondary infection by means of the blood may occur in various infectious diseases such as typhoid fever, meningitis, acute articular rheumatism, pulmonary tuberculosis, pneumonia, and suppurative processes in distant parts of the body.

The only writers who have reported the results of the bacteriological examination of a series of more than ten cases are Dmochowski (1895), Hertzfeld and Hermann (1895), E. Bränkel (1896), and Howard (1898). According to these observers the following micro-organisms are found most frequently in inflammatory conditions of the antra: the streptococcus pyogenes, the staphylococcus pyogenes aureus, albus, and flavus, the pneumococcus, the bacillus of Friedländer, the bacillus foetidus, the bacillus pseudo-diphtheriæ, the bacillus influenæ, and the bacillus pyocyaneus.

Except in the work of Wolff there are no references to the bacteriological examination of the antra in diphtheria and scarlet fever; nor has the relation of these two diseases to inflammatory conditions of the antra been noted clinically. Some text-books state that disease of the antra may occur in the course of or follow the acute infectious diseases, but in none are diphtheria and scarlet fever considered as im-

portant factors. In looking over the clinical histories of the reported cases of disease of the antrum it is occasionally seen that the symptoms date back to an attack of diphtheria or scarlet fever. Thus Farlow (1898) reports a case of catarrhal disease of the antral, frontal, and ethmoidal cavities coming on gradually after an attack of scarlet fever from which the patient had suffered several years before. The bacteriological examination was negative.

Of the 10 cases of antral disease reported by Hertzfeld and Hermann (1895) one occurred in a child thirteen years old, who had had nasal obstruction since an attack of diphtheria seven years previous. The antrum contained a fairly clear fluid in which were thick brownish thready masses. Cultures showed the staphylococcus pyogenes aureus, a yellow sarcina, and a non-pathogenic bacillus.

Bryant (1889) states that empyæma of the antrum may occur in the course of the acute exanthemata, particularly scarlet fever and measles.

Sendziak (1898) reports a case of diphtheria of the pharynx and naso-pharynx complicated by numerous abscesses of the tonsils and abscesses of both antra of Highmore. No bacteriological examination is recorded.

Lothrop (1899) states that diphtheria and scarlet fever may cause acute suppuration of the accessory sinuses of the nose.

The only report of a large number of cases with bacteriological examination is that of Wolff (1895). He examined post mortem the accessory sinuses by Shalle's section in 22 cases of diphtheria, 5 of measles, and 2 of scarlet fever, with the following results :

In all of the *diphtheria* cases changes in the antrum were found. Of 15 severe cases the diphtheria bacillus was found in 12. In 2 of these it occurred alone, in 3 was associated with the pneumococcus, in 1 with the streptococcus, in 2 with staphylococcus pyogenes aureus, and in the others with various combinations of these organisms. In the remaining 7 cases a mild catarrhal condition was found. The streptococcus was found alone in 2 cases, and associated with the staphylococcus pyogenes flavus in 1. The pneumococcus occurred alone in 1 case and associated

with the staphylococcus pyogenes aureus in 1. The latter organism was found with the bacillus pyocyaneus in 1 case.

In 7 cases the sphenoidal sinus was involved. In 2 of these a false membrane was found. The bacillus of diphtheria occurred in 6 of the 7 cases, 3 times alone, and in the other 3 cases with the streptococcus, the pneumococcus, and the staphylococcus pyogenes aureus, respectively. In the seventh case the streptococcus and the staphylococcus pyogenes flavus were found.

In 1 case there was an inflammatory oedema of the frontal sinus. Cultures showed the bacillus of diphtheria and the staphylococcus pyogenes aureus.

In 1 of the 2 cases of scarlet fever the antrum of Highmore was involved. Cultures showed the staphylococcus pyogenes aureus and the bacillus pyocyaneus. In this case there was also an inflammatory oedema of the sphenoidal sinus. A culture was not taken. In the second case there were no inflammatory changes, and cultures taken were sterile.

Of the 5 cases of measles examined, cultures from the antrum in 2 showed the streptococcus and the pneumococcus, and in 1 "staphylococci." The sphenoidal sinuses in these cases were not involved.

These accessory sinuses were examined in 63¹ of our cases.

The cases are divided as follows:

- I. Diphtheria, 52 cases.
- II. Diphtheria complicated by scarlet fever, 7 cases.
- III. Diphtheria complicated by measles, 4 cases.

In no case were there any clinical symptoms pointing to disease of the antra or other sinuses. All cases, with the exception of 3, aged nineteen, twenty-two, and twenty-four years respectively, were children. Of the latter, 2 were ten and 1 twelve years old. All others were between two and six years of age. Most of the cases in which the sinuses were invaded died between the fourth and tenth days of the disease; the average was 9 days. The earliest infections occurred in diphtheria on the second and third days after the appearance of the membrane.

Methods. — The nasal sinuses were examined by Harke's section, which consists (after removing the brain) in sawing

¹ Forty-six of these cases have been previously reported: Pearce, The Bacteriology of the Accessory Sinuses of the Nose in Diphtheria and Scarlet Fever. Jour. Boston Soc. of Med. Sciences, March, 1899.

through the base of the skull and forcibly separating its two halves. The frontal and sphenoidal sinuses are thus exposed, and the antra of Highmore are easily reached by chipping away the turbinated bones on either side. This method naturally alters the appearance of the contents of the frontal and sphenoidal sinuses. In this series, however, it has made little difference in the results, for the cases were mostly young children in whom the sinuses were but slightly, or not at all, developed. In those cases in which they were developed, and exudation was found, smears were made at once in order to control the cultures.

In opening the antra the turbinate bones were cleansed as much as possible, and care was taken not to introduce particles of mucus with the knife used to chip away the bone. Cultures were made from the interior of the cavity with a thin platinum needle. Smears for the control of the cultures were also made.

As the chief object of this investigation was to determine the condition of the antra, rather than of the other sinuses, every precaution was taken to prevent contamination of these cavities, and the results here reported are as nearly accurate as is possible by any method of examination. In regard to the frontal, sphenoidal, and ethmoidal sinuses only those cases of infection were accepted as conclusive in which there was a definite exudate and in which the results obtained by smears and cultures were the same.

All primary cultures were made on Loeffler's blood serum.

In some cases the lining membrane of the antrum was removed for histological examination.

Diphtheria. — Fifty-two cases examined. In 33 inflammatory changes were present in the accessory sinuses, as follows:

Both antra, 19.

Both antra, sphenoidal and ethmoidal sinuses, 2; one antrum only, 9; sphenoidal sinuses only, 2; sphenoidal and ethmoidal sinuses, 1.

Of the 21 double antral cases the exudate, on both sides, in 5 was a thick yellow pus; in 3 a seropurulent fluid; in 3

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In 1 case there was a general infection with the streptococcus; in the other a streptococcus infection of the middle ear.

In the case with purulent exudate in the sphenoidal and ethmoidal sinuses, the streptococcus was found.

Diphtheria with measles, 4 cases. The antra in each case contained a sero-purulent fluid. The diphtheria bacillus and the streptococcus were found in 2; the streptococcus alone in 1; and the diphtheria bacillus alone in 1.

Diphtheria with scarlet fever, 7 cases. In 5 of these the antra were normal, and in 2 inflammatory changes were found. Of these 2 cases 1 was unilateral and contained a thick purulent fluid. Cultures showed the diphtheria bacillus and a variety of unrecognized bacteria.

In the second case one antrum contained a thin mucoid fluid and the other a thick creamy fluid. Cultures from both contained the streptococcus, and the latter the staphylococcus pyogenes aureus also. The sphenoidal and ethmoidal sinuses were also involved, containing thick creamy pus in which the streptococcus was found. In this case both middle ears contained purulent contents. Cultures showed the diphtheria bacillus and the streptococcus.

Histological examinations. — In 5 cases in which the contents were mucoid or but slightly purulent, and in 3 in which they were purulent and contained shreds of false membrane, the lining membrane was stripped off for histological examination. In the former the changes were slight. The tissue beneath the epithelium was œdematous, and here and there were a few lymphoid and plasma cells and an occasional polynuclear leucocyte.

In the other 3 cases a definite false membrane composed of fibrin and leucocytes was present.

Conclusions. — The preceding cases indicate that infection of the antrum of Highmore is quite common in fatal cases of diphtheria and scarlet fever. The micro-organisms found are the diphtheria bacillus, the pneumococcus. In some cases the exudate is sero-purulent, in others distinctly purulent.

fibrinous membrane had formed. In 7 cases a mucoid accumulation only was found. In the cases here reported the inflammatory changes in the antra did not produce symptoms sufficiently marked to attract attention during life. If symptoms did exist they were probably referred to the primary disease.

The practical point in regard to this subject is to determine whether this infection takes place as commonly in those cases which recover as in those which are fatal; and, if it does, whether it may not lead to subacute or chronic disease of the accessory sinuses. In fatal cases with a diminished distance to bacterial invasion, as shown by the large number of cases with inflammation of the middle ear and frequent systemic infection, an infection of the antrum is not surprising. It is very probable, however, in view of its frequency in fatal cases, that it may occur in some cases which recover. In most of these cases it probably clears up without any ill effects, but it is very possible that in others it may so alter the condition of the lining membrane that later an acute inflammatory condition in the nose may readily set up chronic nasal disease.

That the infection of the antrum with diphtheria bacilli explains the persistence of these bacteria in cultures from the nose long after all evidence of membrane has disappeared seems very probable. Any one who has made routine bacteriological examinations of the throat and nose in diphtheria can recall cases in which positive cultures were obtained from the nose for weeks and even months after all evidence of the disease had subsided. In the laboratory of the Boston City Hospital, where no case of diphtheria is discharged until three negative cultures have been obtained from both throat and nose, cases have been detained for six, seven, eight, and nine weeks, and even three months, on account of the persistence of diphtheria bacilli in the nose.

Le Gendre and Pochon (1895) report a case in which they obtained positive cultures from the nose for fifteen months after nasal diphtheria. Upon douching the nose with antiseptic solutions the bacilli would disappear; but as soon as

the cleansing was stopped the bacilli would cultures. The writers claim that the bacilli the deep glands of the mucous membrane, septics could not reach them. In view of reported it would seem much more probable case with infection of the antrum. The antrum. If it becomes infected with diphtheria bacilli not obstructed, cultures from the nose would show these bacilli until the cavity is completely the organisms have died out. In all cases, therefore the diphtheria bacillus persists in cultures following examination of the antral cavities would be indicated.

MIDDLE EARS.

The diphtheria bacillus has been found in the middle ear by Councilman and Wright. Councilman reports 3 cases. In all of Wright's cases the diplococcus and in one case reported by Stephens and Lommel the diplococcus also were present. Lommel reports diphtheria, in 24 of which there was disease of the middle ear. In only 1 of these cases was a bacteriological examination made. The diplococcus lanceolatus was found in 1 case. Councilman reports a fatal case of pyæmia, the source of which was a suppurative middle ear following diphtheria. "Large numbers of cocci" were found.

Podack in 3 cases of diphtheria complicated by middle ear disease found the diphtheria bacillus and the streptococcus in the middle ear. In 1 case there was a definite perforation of the membrana tympani; the other two were purulent.

Baginsky has found diphtheria bacilli associated with the streptococcus and the pneumococcus in the middle ears.

The middle ears were examined in 144 cases. In 86 cases disease of the middle ear was found. In 10 cases exudate was found in one or both ears in 10 cases the exudate was purulent. The middle ear was involved on both sides in 7, and on only one

In 2 cases the exudate was more mucoid than purulent, and the mastoid cells were not involved at all. In 4 of these cases the condition was bilateral. In 3 cases the exudate was mucoid on one side, and purulent on the other. Of the 44 purulent cases, 35 were double. In 7 no cultures were taken. In the remaining 28, the diphtheria bacillus occurred in both ears in 9 cases, in only one in 6 cases. The streptococcus occurred in both ears in 17 cases, and in only one ear in 3.

The staphylococcus aureus occurred in both ears in 4 cases, and in only one ear in 3. The pneumococcus occurred in both ears 5 times. The staphylococcus albus occurred in 2 cases. The streptococcus pyogenes alone was found in both ears in 7 cases, the staphylococcus aureus alone in 1 case, and the pneumococcus alone in 1 case. Generally a combination of two or more of these organisms was found, as a rule the diphtheria bacillus with the streptococcus, or with the staphylococcus aureus, or with both.

In the 9 cases with purulent exudate in one ear only, cultures were taken in all but 1 case. The streptococcus occurred 5 times, the diphtheria bacillus and the staphylococcus aureus each 4 times, and the diplococcus lanceolatus once. The streptococcus occurred alone twice, the diphtheria bacillus alone once, and the staphylococcus alone once. In all other cases a combination of two or more organisms occurred.

Of the 4 cases with mucoid material in both ears, cultures were taken from 3. The staphylococcus aureus was found alone in 1 case, and with the diphtheria bacillus in 1 case. The latter occurred alone in the third case.

In the single cases (8) no cultures were made in 2 cases; in the others the diphtheria bacillus occurred 3 times, the streptococcus 5 times (twice in pure culture), the staphylococcus aureus twice, and the bacillus pyocyaneus once.

In Group II. there were 27 cases, 23 of which were purulent, with involvement of the mastoid cells of both ears in 3, and of those of only one ear in 6. Seventeen of the purulent cases were double, and 6 single. In the double cases the diphtheria bacillus occurred in both ears 11 times, in only one ear once. The streptococcus occurred in both ears 10

times; in one ear 4 times. The staphy aureus occurred in both ears 3 times; in c bacillus pyocyaneus occurred in 2 cases. of the above micro-organisms occur in pu case no cultures were taken.

Of the 6 single cases, in 3 no cultures the diphtheria bacillus occurred alone; in cus alone; and in 1 both these micro-orga

Of the 4 mucoid cases 3 were bilateral were sterile; the other 2 showed the strep one, and associated with the diphtheria ba in the single case both these micro-organism

It is not to be understood that in th micro-organisms mentioned were the only some, various non-pathogenic organisms w those known to be pathogenic. Several lated and studied, but none showed pat when inoculated into guinea-pigs or rabb of these organisms is readily explained munication of the middle ear with the r Eustachian tube. This also explains th occurrence of the diphtheria bacillus. W histological examination of the mucous the absence of this it is impossible to say bacilli were the cause of the exudation. may have been caused by the associated p and the diphtheria bacilli may have been present.

It is of interest that in only 23 of the condition recognized during life. For th cult to estimate the stage of diphtheria at of the middle ear is most liable to occur. 6 developed before the fifth day, 8 betw eleventh days. The remainder developec 2 as late as the thirty-fourth day. With cases all of these cases were in children of age. Nasal diphtheria was present in

LATERAL SINUS.

In 1 case of Group I. *thrombosis* of the lateral sinus followed suppuration of the middle ear and mastoid cells. Cultures from the thrombus showed the streptococcus and the diphtheria bacillus. Cultures from the mastoid showed the same organisms and also the staphylococcus aureus.

PERIOSTEUM.

Acute periostitis. — In a case of Group II. (diphtheria with measles) there was found beneath the periosteum of the parietal bone a small accumulation of pus. In cultures the diphtheria bacillus and the streptococcus were obtained.

ACUTE ABSCESES IN VARIOUS SITUATIONS.

In Group I., 7 cases were noted: 3 of these were in the cervical lymph nodes, and in 2 of them were found the diphtheria bacillus and the staphylococcus albus. The third case was due to the streptococcus and the staphylococcus aureus, as was also a retropharyngeal abscess. An abscess of the scalp contained the staphylococcus pyogenes aureus, and one in a bronchial lymph node the streptococcus. A tonsillar abscess contained the staphylococcus albus and the diphtheria bacillus.

In Group II. 14 abscesses were examined. Nine were of the cervical lymph nodes, and in 5 the streptococcus was found in pure culture. In 2 the diphtheria bacillus occurred associated in one with the streptococcus and in the other with the staphylococcus aureus. The abscesses in the other two had been opened and dressed antiseptically; cultures, therefore, were not taken. A retropharyngeal abscess contained the diphtheria bacillus, the streptococcus, and the staphylococcus aureus, while a laryngeal abscess contained the streptococcus and the staphylococcus. A retrolaryngeal abscess contained the streptococcus. An abscess of the spleen with an associated peritonitis was due to the streptococcus, as was also an accumulation of pus over the trochanter of the femur.

Acute abscesses containing the diphtheria bacillus have been reported as follows: In abscesses of finger in pure culture by Leary; diphtheria bacillus and staphylococcus aureus in paronychia of toe by Wright; of the larynx by Goris; of the thumb (paronychia) by Müller. The abscesses occurring in the course of diphtheria are generally due, however, to pyogenic cocci, particularly streptococci. According to McCollom, abscesses forming at the point of injection of antitoxin are generally due to the streptococcus pyogenes, although Wright reports one case in which the diphtheria bacillus was found.

PATHOLOGY.

MEMBRANE.

Distribution of membrane. — A definite membrane which varied in its extent and distribution was found in 127 of the 200 cases examined. Membrane was found on the tonsils in 83 cases, epiglottis 60, larynx 75, trachea 66, pharynx 51, mucous membrane of nares 43, bronchi 42, soft palate, including uvula 13, œsophagus 12, tongue 9, stomach 5, duodenum 1, vagina 2, vulva 1, skin of ear 1, conjunctiva 1. The membrane was most frequent in the larynx, and next in order of frequency come the trachea, tonsils, epiglottis, and pharynx. In a number of cases but a small amount of membrane limited to a single situation was found. It was found on the tonsils alone in 7 cases, trachea 2, larynx 3, pharynx 1, soft palate 1, œsophagus 1, epiglottis 2, mucous membrane of nares 1.

In all other cases several structures were involved. These may be divided as follows, according to the extent of the membrane:

Twenty-two cases in which membrane was present on tonsils, on nasal passages, on either pharynx or palate, or both, with extension to some part of lower air passages. These cases were those with the most extensive distribution of the membrane and included the following unusual locations: tongue 6, œsophagus 5, stomach 3, conjunctiva, skin, vulva, and vagina, each 1 case.

Three cases, membrane present on tonsils, nasal passages, and some part of lower air passages. These include 1 case with involvement of stomach and duodenum, and 1 of tongue.

Three cases, membrane present on tonsils, nasal passages, pharynx or palate, or both.

Three cases, membrane on tonsils, pharynx, or palate, including 1 case of membrane on œsophagus.

Sixteen cases, membrane on tonsils, pharynx or palate, or both, and some part of lower air passages. This includes 2 cases in which the tongue and 1 in which the œsophagus were involved.

Ten cases, membrane on tonsils with some part of the lower air passages.

Seven cases, membrane on nasal passages with some part of the lower air passages, including 1 case with involvement of œsophagus.

Seven cases, membrane on pharynx and some part of lower air passages.

Thirty-one cases, membrane on some or all of lower air passages, including 1 case of involvement of œsophagus and 1 of the stomach.

Two cases, membrane on nasal passages, pharynx, and palate; in 1 case the œsophagus was involved.

One case, membrane on pharynx and œsophagus.

One case, membrane on nasal passage and vagina.

The following are the 2 cases with the most extensive and unusual distribution of the membrane :

B. C. H., '97. 184. Woman, thirty-five years old. There is a membrane covering both nasal and buccal surfaces of the soft palate and uvula extending over the vault and back of pharynx, and including the tonsils, which show in addition central losses of substance. On the back of the tongue there are a few patches of membrane which is thick, yellow, rather adherent, and extends over both surfaces of epiglottis where it is very thick, into the larynx, trachea, and bronchi. In the lower air passages the membrane is thin, white, and easily removed; where there is no membrane the surface is deeply injected and granular. The bronchi and trachea are filled with frothy serous fluid, and the membrane is adherent only over small areas.

Lung. — On section the larger bronchi are completely filled with yellowish, purulent, and fibrinous plugs.

The smaller bronchi have softer puriform contents. Associated with this condition is a bronchopneumonia.

In the œsophagus there is a continuation of the membrane from the pharynx. In the upper portion the membrane is thick, grayish-yellow, and rather evenly distributed over the surface. Below it is thinner and

occurs in longitudinal streaks. Approaching the stomach it is found in small patches partly covering longitudinal eroded areas which are deeply injected and granular. The erosion stops sharply at the cardiac orifice.

Genitals. — The inner surface of the labia majora, the labia minora, the vestibule, and the introitus are covered with a thick, greenish-yellow, slimy, opaque pseudo-membrane which is very adherent. This membrane extends for a short distance into the vagina, where it merges into a slightly injected area which is followed by apparently normal mucous membrane. Beyond this the vault is covered by a thin gray semi-transparent membrane which is not adherent, and extends up over the vaginal surface of the cervix. Uterine mucous membrane normal. Membrane stops sharply at the meatus urethrae. Bladder and urethra normal.

B. C. H., '97. 215. Age seven years. Inspection of the upper nasal cavity shows mucous membrane injected, of deep purple color, and middle and lower turbinates covered with yellow, soft membrane. The membrane also involves the nasal surface of the soft palate as well as part of its buccal surface. The tonsils, pharynx, and extreme upper portion of oesophagus are covered by a thick, ragged, greenish pseudo-membrane which is rather adherent. This membrane extends deeply into the follicles of the tonsils, and on section there is deep necrosis of the tonsillar tissue. In the trachea the membrane becomes much thinner. It is smooth, pale yellow, and easily removed. Mucous membrane beneath deeply injected and granular. Membrane can be followed beyond the second divisions of the bronchi. Lung on section shows the large bronchi completely filled with gray fibrinous plugs.

Stomach. Beginning sharply at the cardiac orifice, the mucous membrane is slightly eroded in irregular longitudinal patches. These patches in places are covered by distinct yellow fibrinous membrane which is rather adherent, and leaves a red granular surface on removal.

The following cases of stomatitis and cancrum oris due to diphtheria bacilli are taken from the clinical records:

1. Simple *stomatitis* occurred in 5 cases. Three were cases of diphtheria with measles, 1 of diphtheria with scarlet fever, and 1 of diphtheria only. All were in children under four years of age. Three developed before the ninth day, the other two on the thirteenth and thirty-second days respectively.

2. *Cancrum oris*, 2 cases. Both two years old. Both were cases of diphtheria with scarlet fever and measles. In one case stomatitis occurred on the fourth day, ulceration on seventeenth day, and finally involved the entire cheek and a portion of the upper jaw. Death on thirty-first day. In the other case stomatitis on the sixth day, ulceration of cheek on fifteenth day.

The following cases of conjunctivitis are taken from the clinical records:

1. True *diphtheritic conjunctivitis* (with membrane), 2 cases. In one case membrane disappeared before death. Positive cultures from eye in both cases. Scarlet fever in both cases. Diphtheria of nose in one. One aged fourteen months, the other three years.

2. *Muco-purulent conjunctivitis* with presence of diphtheria bacilli (no membrane), 3 cases. Diphtheria of nose in all three cases. All under three years of age. All developed before the seventh day.

The character of the membrane varies. It may appear as a thick mass of a brownish or grayish-brown or almost black color, or as a thin whitish pellicle. It may extend as a continuous mass over the tonsils, palate, pharynx, epiglottis, larynx, and trachea, or only small isolated patches may be found. It may be granular and easily broken up or dense and elastic, and may be removed in large patches. It is always more easily removed from the trachea than from any other part. On opening the trachea it often appears as a loose wrinkled mass lying in the lumen. Removal of the membrane from the trachea or larynx, even when it is thick and adherent, rarely leaves a loss of substance extending into the subepithelial connective tissue. The tissue beneath the membrane and in the vicinity is intensely injected and often hæmorrhagic. This injection is always evident on microscopic examination, but it may be obscured on macroscopic examination by superficial necrosis, and may be more evident in foci.

The *literature* on the histological characteristics of the membrane and its mode of formation is not extensive. Virchow sharply separated the croupous from the diphtheritic membrane. In the formation of the croupous membrane according to him the fibrin in the plasma is greatly increased, the exudate passes through the epithelial covering and coagulates on the surface. Such a membrane may be formed on all surfaces covered with mucous membrane, but is seen best on the respiratory mucous membrane. In the diphtheritic membrane the exudate consists of coagulated amorphous fibrin and lies in the upper layers of the mucous membrane.

The exudate coagulates between the tissue elements, and if it extends over the surface of the connective tissue it lies beneath the epithelium. There is necrosis of the tissue combined with the exudation and no new cells are formed in the diphtheritic membrane, though they are formed in the croupous.

A material advance in our knowledge of the histogenesis of the membrane was made by E. Wagner. He believed that the membrane formation was chiefly due to a peculiar metamorphosis of the epithelium. In this process the protoplasm and the nucleus of the epithelial cells become enlarged and small vacuoles are formed both in the centre and periphery of the cell. The nucleus disappears and the cells become converted into large thick masses containing round and oval spaces which give to each cell an appearance which he compares with the horns of a stag. From the fusion of adjoining cells a reticular membrane is produced. The croupous membrane is produced in the same way as the diphtheritic, the only difference being that in croup the membrane is composed of finer fibrillæ of fibrin and encloses more cells than the diphtheritic membrane. Cornil and Ranvier confirmed completely the observations of Wagner. They isolated the altered epithelial cells, stained them with picrocarmine, and decided that they did not contain fibrin but a material similar to mucin. Hartman regards croup and diphtheria as identical processes. The plasma poured out in the mucous membrane is forced to the surface by the contraction of the muscles of the pharynx and coagulates, forming a croupous membrane. If the exudation continues, the membrane already formed causes it to accumulate in the tissue and coagulate, producing diphtheria.

Weigert does not recognize the anatomical distinction between croup and diphtheria which Virchow has made. According to him, in croup of the trachea, in which the membrane is easily removed, the exudate is seated on the surface bare of epithelium, though it may extend over the epithelium adjoining. There is a pseudo-diphtheria in which the membrane lies on the connective tissue surface just as in croup,

but is more firmly attached to it. In true diphtheria the superficial layers of the connective tissue are converted into a mass similar to coagulated fibrin. Diphtheria may be found in any of the mucous membranes except the trachea. The membrane formation is due to a combination of coagulation necrosis and fibrinous exudation, both the necrotic cells and the fibrin contributing to it. The necrotic pus cells play a greater part in its formation than do the epithelial cells.

Senator also distinguishes several forms of diphtheria. There is a catarrhal form in which the lesions are the same as in a simple catarrh. The next is a pseudo-croupous form which is found only in the larynx and in which small whitish points, which are easily removed, are seated on the surface in which there is a catarrhal inflammation. The true diphtheria is the third form, and in this the membrane clings firmly, and when removed leaves a bleeding surface.

Peters studied the formation of the diphtheritic membrane under the direction of v. Recklinghausen. He believes that the thick dense refractive membrane in diphtheria is formed by a hyaline degeneration of the cells both of the epithelium and of the exudation. Hyaline formation is seen also in the blood-vessels and lymphatics of the connective tissue beneath the membrane. The croupous membrane is formed by a fibrinous exudation only; the hyaline degeneration takes no part in it. In the ulcerating form of diphtheria but little hyaline is present.

Rindfleisch says that the diphtheritic membrane does not consist of ordinary fibrin. When small pieces of the dense membrane are laid in weak ammonia and t, the membrane is found to be composed of c cells united to one another. In the beginning of on the cells are round and the membrane often si com- posed of round balls united to each other. h this degeneration there may be interstitial fibr n be- tween the degenerated cells. This is mor n the trachea than elsewhere.

Orth was the first sharply to differentiate two distinct forms

of structure in the membrane, one a membrane formed by exudation, composed of a meshwork of fibrin enclosing leucocytes and most often found in the trachea and bronchi; the other a membrane formed by hyaline fibrinoid degeneration of the leucocytes and epithelium. This latter membrane is thick, elastic, and adherent, and is composed of a thick dense hyaline reticulum similar to young osteoid tissue. Large hyaline balls or irregular masses may be found in the membrane. This dense membrane is found chiefly on the tonsils and pharynx; the reason for this is that more leucocytes are in the exudate in these places. In the trachea the dense basement membrane prevents their passage into the exudate. The adhesion of the membrane on the tonsils and pharynx is favored by the irregularities of the surfaces and the presence of lacunæ. The membrane clings more closely to the surface of the epiglottis than elsewhere in the air passages. The reason the membrane is so easily separated from the surface of the trachea is that it is forced up by the secretion of the mucous glands beneath it.

Ribbert considers the hyaline membrane as due to a hyaline metamorphosis of the fibrin, and says that the hyaline masses may be continuous with fibrillæ of ordinary fibrin. The membrane may be seated on the surface or may extend into the tissue. Leucocytes and epithelial cells are often enclosed in it.

Oertel in his monograph describes the membrane as composed of a coarse reticulum which forms the chief mass, of a finer reticulum with membranous branchings, and of a dense, broad, refractive reticulum which differs from the others in staining strongly with methylene blue and fuchsin. He thinks this membrane is formed by a peculiar degeneration of the round cells. He describes also a direct division of the nuclei of the epithelial cells in the early stage of the process. Heubner investigated the formation of the diphtheritic membrane by removing small pieces from the tonsils and pharynx during life. In the earliest stage of the process he found a coagulated exudation in the upper part of the epithelium between the horny cells, which were pushed

apart. The membrane, at first composed of coagulated exudation, becomes changed at the end of the second day into a peculiar refractive reticulum. Baumgarten comes back to the views of Wagner in giving the chief place in the formation of the membrane to the hyaline metamorphosis of the tissue elements. The fresh diphtheritic deposit on the mucous membrane of the pharynx consists of the swollen elements of the epithelium which have lost their nuclei and become changed into a substance similar to fibrin. The degenerated epithelium becomes converted into a refractive network similar to that described by Wagner. The nodal points in the reticulum are formed from the remains of the epithelial cells. Leucocytes are rare and show no trace of this formation. A fibrinous exudation consisting of fine fibrillæ of fibrin, in whose meshes numerous leucocytes and red blood corpuscles are contained, may be formed beneath this membrane. When the process extends into the connective tissue beneath there is a fibrinoid metamorphosis of the connective tissue similar in character to that taking place in the epithelium. He speaks of this as desmoid pseudo-fibrin. There may be some exudation fibrin in the connective tissue which can be distinguished from the desmoid pseudo-fibrin by the finer fibrillæ and the less marked refraction. After the first membrane is cast off a second membrane may be formed from exudation-fibrin and cells. The connective tissue which has undergone such a fibrinoid metamorphosis is not to be regarded as destroyed, but may again return to the normal condition.

Baginsky recognizes three layers in the membrane: on the surface a layer composed of loose necrotic epithelium and round cells; next to this a wide fibrinous or fibrinoid network, rather denser toward the surface, containing scattered epithelial and round cells; and lastly a layer composed of altered epithelial cells between which there is a dense fibrinous network.

Middeldorpf and Goldman come to the following conclusions: Both in experimental croup and in epidemic diphtheria fibrin forms the essential constituent of the false

membrane and comes as an exudation from the vessels of the inflamed mucous membrane. The formation of the pseudo-membrane takes place after the complete destruction and desquamation of the epithelium. The hyaline material found in the dense refractive membrane is not a special substance, but is a derivative of the fibrin. The croupous and diphtheritic membranes are both in their mode of origin and composition completely homologous structures.

Neuman in an article on the fibrinoid degeneration of the connective tissue says that the diphtheritic membrane may be in large part due to a direct transformation of the upper layers of the connective tissue into fibrin.

With regard to relation of the bacilli to the formation of the membrane Henka has found that a membrane similar to that found in man is produced when the bacilli are rubbed on the mucous membrane of the trachea. Other micro-organisms produced no membrane. Roger and Bayeux found that the diphtheria toxin is in itself capable of producing a membrane. Baumgarten denies that the bacilli alone are capable of producing the membrane, but claims that their action is assisted by the other pyogenic organisms invariably present.¹

On examination of the membrane from a large number of cases of diphtheria the variety in structure which it presents is striking. The membrane on the tonsils (Plate XV., Fig. 1 a) will be described first because the variations in structure are best seen there. We can distinguish microscopically two distinct varieties of the membrane corresponding to the differences observable macroscopically. The dense, firm, elastic membrane which can be stripped off in large flakes is composed of a reticular structure, with considerable uniformity in the size of the beams which form the reticulum. (Plate XV., Figs. 3 and 4.) Occasionally, particularly in the upper part of the membrane, there are small areas in which the beams

¹ We regret very much that we have had no opportunity of investigating any of the cases of membrane formation which clinically occur so frequently in the pharynx without the diphtheria bacilli being present. In every case of membrane formation on the tonsils or pharynx seen at autopsy the diphtheria bacilli were present.

of the reticulum are large and the spaces extremely small. This tissue is much denser and more refractive both in the stained and in the unstained condition than is ordinary fibrin. The reticulum takes the fibrin stain in most cases, but shows a marked difference when compared with the stain of pure fibrin. With iron hæmatoxylin it takes in some cases the dense black color which fibrin gives with this stain (Plate XV., Fig. 4); in other cases it is tinted only a bluish-gray (Plate XV., Fig. 3), or there may be a difference in the color reaction; the centres of the fibres may be pale, while the outer portions stain intensely. With methylene blue and eosin it takes more of the blue than of the eosin stain; with fuchsin it stains intensely red; and it is deeply but also irregularly stained with Weigert's fibrin stain.

The reticulum in most cases is homogeneous in structure, and the beams composing it have the same size. In other cases nodular projections are found along them, or they may contain small cavities. (Plate XV., Fig. 4.) In one case a membrane was found so dense that it appeared as a solid mass with small canals intersecting it. The spaces enclosed by the reticulum vary but slightly in size. They may be angular or round, for there may or may not be thickening of the reticulum at the points of contact. When this membrane is present, masses of material of the same character as the reticulum and of varying size may be found which are either enclosed in the reticulum or lie in its vicinity. (Plate XV., Fig. 3.) These masses are often continuous with the reticulum. They often stain irregularly, but rarely give the intense fibrin stain which the reticulum does. Usually there is only a small area around the periphery which gives the black stain of fibrin; the centre stains the bluish-gray color which parts of the reticulum take. In some an irregular intensely staining mass is seen in the centre, in others again the centre is unstained. The masses are usually of about the same size as the epithelial cells, and where parts of the epithelium remain they may be continuous with it. In the smaller masses an irregular mass of nuclear material resembling the nucleus of a polymorphonuclear leucocyte may be

und. There would seem to be little doubt from the transitions which may be observed that these masses which have been noted by various observers are epithelial cells and leucocytes which have undergone hyaline degeneration and may play an important part in the formation of the hyaline membrane. Very few cells are found in the spaces of the reticulum, although occasionally there is present an entire leucocyte or the fragment of a nucleus. A membrane of this character may cover the entire surface of the tonsil, or only fragments of it may be found enclosed in fibrin, or it may form the upper part only of the entire membrane, being separated from the tissue beneath by fibrin. The upper surface of the membrane is rarely sharp, the reticulum here becomes swollen and more or less disintegrated.

The other variety of membrane which macroscopically is characterized by greater friability is composed of fibrin. (Plate VI., Figs. 1 and 4, and Plate XVII., Fig. 1.) The difference between the two can be recognized at a glance even under low power. The fibrin forms a reticulum just as does the hyaline material, but varies greatly in the size of the fibres and the spaces. In general the spaces are larger than in the hyaline membrane and more often oblong than round, with the long diameter parallel with the surface. The reticulum often appears to be arranged in whorls starting from a centre. In the spaces of the fibrin there are numerous leucocytes, sometimes well preserved, at others represented only by cell and nuclear detritus. When well preserved they usually can be recognized as polymorphonuclear in character. In some cases the fibres of the network are thick, and extending from these thicker fibres is a network of very fine fibrillæ. This fibrinous membrane often is continuous over the entire surface of the tonsil and extends into every crypt. The hyaline membrane is never found extending from the surface into the crypts, though occasionally small masses of hyaline reticulum are found in them.

The epithelium is usually absent beneath the membrane. In places small masses of epithelium consisting of the lower layers of cells are found (Plate XVI., Fig. 1), and in places

the membrane may extend over a considerable area of epithelium which is but little altered, although the upper layers of cells are always absent. (Plate XVII., Fig. 2.) We have never found a case in which the membrane extended over a large surface of intact epithelium. Both sorts of membrane, but especially the fibrinous, often show areas which differ from the general character of the membrane. Areas are found where the reticulum is broken and forced apart. The spaces thus formed are filled by a fibrinous network, the fibres of which are finer than the remainder, the spaces larger and more irregular and containing large numbers of leucocytes. The membrane proper may be elevated from the surface by such a formation. The line separating the old membrane from the new formation below it is easily seen. It is obvious in these cases that after the membrane is formed an exudation which afterwards undergoes coagulation may enter into it, forcing apart its meshes or elevating it bodily.

When the membrane extends over the epithelial surface it is rarely in contact with it, but is separated from it by a space containing granular material, leucocytes, and nuclear fragments. (Plate XVII., Fig. 2.) The exudation seems in some cases to flow over the surface like lava reaching a certain distance before becoming solidified, but the membrane may be added to by exudation coming through the epithelium and coagulating on contact with it.

In such cases appearances similar to the smallpox vesicles may be seen. The upper layers of the epithelium may be elevated, forming vesicles filled with fibrin and pus cells, or small masses of adherent epithelium. The vesicles are often divided by small septa formed by adherent epithelial cells (Plate XVII., Fig. 2.) That there is an abundant exudation passing through the epithelium in the vicinity of the membrane is shown by vesicles filled with coagulated exudation with or without fibrin beneath the epithelium or above the first layer of cells.

Almost invariably the epithelium beneath the membrane and in the vicinity of it shows various alterations. It contains numbers of polynuclear leucocytes and lymphocytes. (Plate

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In other places they seem but little changed. The epithelium lining the crypts in all cases is loose, œdematous, and infiltrated with cells. In many cases it is difficult on superficial examination to distinguish the epithelium from the tissue beneath. The cells are small, the nuclei resemble lymphoid cells, and where they are separated from one another and infiltrated with cells it is difficult to distinguish the epithelium from the infiltrating cells. In all of these places the flat epithelial cells of the surface are cast off and masses of them lie inside the crypt. Among the lymphoid cells in the epithelium there are numbers of plasma cells, sometimes single, more often in groups. The blood vessels of the papillæ extending into the epithelium are surrounded by lymphoid and plasma cells. The lymphoid and plasma cells, like the red blood corpuscles, seem to be carried for the most part into the epithelium by the exudation stream. They most generally are found in the deeper layers where the epithelial cells are separated from each, though occasionally single ones are found nearer the surface in the same position as the polynuclear leucocytes. In some cases the crypts are dilated, the epithelium almost entirely absent, and the space filled with polynuclear leucocytes. In such places there is but little fibrin.

The tissue beneath the membrane, and beneath the epithelium when this is present, is variously altered — the most profound alteration consists in necrosis with dense fibrinous exudation; in this case the fibrin in the tissue is so mingled with the fibrin on the surface that it is difficult to see where the tissue begins. The fibrin in these cases is in the form of a fine reticulum with small spaces which are either empty or contain nuclear fragments. The fact that this is tissue and not membrane is often only to be recognized by the presence of denser areas representing the vessels. In other cases there is a dense hæmorrhagic infiltration of the surface with masses of red blood corpuscles mixed with the fibrin. The tissue in these places is not evident. In other places again there is a slight extension of the membrane into the tissue in the form of small patches of fibrin. A process very analo-

gous to the hyaline degeneration of the epithelium may take place in the tissue, but is less often found in the tonsil than in the epiglottis and trachea.

In one specimen there were beneath the almost intact epithelium of a crypt small hyaline masses, and masses of fibrin which were applied to the bottom of the epithelium and extended from this into the tissue. The hyaline material could be distinguished from the fibrin by the size of the reticulum, and the manner of staining. (Plate XVI., Fig. 3.) The fibres were larger and more refractive. The hyalin was present, both in the form of a reticulum and in masses. The refractive hyaline material, just as in the formation of the hyaline membrane on the surface, seems to be formed by a direct metamorphosis of the tissue. (Plate XVI., Fig. 2 e.) The first change leading to this is swelling of the tissue accompanied by disappearance of the fibrillar character. The homogeneous mass so formed becomes more opaque and hyaline, and the whole or portions of it take the fibrin stain. Definite fibrin in the form of a fine reticulum passes directly into the hyaline material. A considerable amount of fibrin also is found in the tissue with no connection with the membrane, and often with no apparent connection with necrotic tissue.

This hyaline fibrinoid degeneration of the connective tissue is more marked in the epiglottis than in the other tissues. In this degeneration it does not seem to us that the tissue, as such, is directly converted into fibrin. The fibrin coming from the fibrin factors in the exudation is simply deposited in the tissue, which is probably necrotic, and which has undergone first a hyaline metamorphosis.

This is the desmoid pseudo-fibrin described by Baumgarten. Occasionally both sorts of membrane are found together, the upper part distinctly hyaline, and beneath this a fibrinous reticulum. This seems due to the elevation of the primary hyaline membrane by the accumulation beneath it of a fibrinous exudate. Such an exudate can be distinguished from the primary membrane even when it is of the same character by the large size and irregularity of the fibrin network. In still other cases the membrane is elevated by an exudate

containing no fibrin, and showing only as a granular coagulated material.

The changes in the trachea in connection with membrane formation are in many respects different from those in the other tissues. In general the membrane is distinctly fibrinous. (Plate XVI., Fig. 1.) Only in one instance in an early and very acute case in a child one year old was the membrane hyaline, and this only in places. This hyaline membrane differed from that on the tonsils in the very small size of the spaces in the reticulum. In the fibrinous membrane the reticulum is much closer than in similar membrane elsewhere. The meshes are almost always flattened and the long diameters of the spaces are parallel to the surface. Three more or less distinct layers can be distinguished in the membrane. On the surface is a rather granular mass composed of nuclear detritus and broken-up fibrin in which no trace of reticulum can be seen. Beneath this lies the definite fibrinous reticulum with small and generally flattened spaces. The beam-work of the reticulum offers little or no variation in size. In some cases the reticulum is filled with cells which are almost exclusively polynuclear leucocytes with an occasional red blood corpuscle. The cells in some cases are comparatively well preserved in form, though the nuclei are broken up and degenerated; in other cases only fragments of the cells and nuclei can be distinguished. Between this network and the membrana propria, and frequently separated from the former by a denser mass of fibrin, is a layer in which the spaces in the fibrinous network are much larger. This layer shows a rather definite architecture. Thicker masses of fibrin from the membrane above pass through perpendicularly to the membrana propria, to which they adhere, and from these lateral communicating fibres are given off. In the meshes of this fibrin are numbers of cells, sometimes single, sometimes in slightly coherent masses. (Plate XVI., Fig. 1.) Along the membrana propria they usually are arranged in a row side by side. As a general thing only the nuclei can be recognized, and the character of these shows them to be epithelial. The nuclei also show the swollen vesicular

form and the peripheral arrangement of chromatin which we have described in the tonsil.

In the cell groups nuclear masses resulting from direct segmentation are seen. There seems to be little doubt that in the trachea in most cases there are remains of the epithelium beneath the membrane, but the membrane is never seen extending over large areas of comparatively intact epithelium, as in the tonsils and pharynx. Among the remains of the epithelial cells are a very few red blood corpuscles and an occasional lymphocyte. The very small number of red corpuscles found in the membrane evidently is due to the barrier to their passage which is offered by the membrana propria, for the tissue beneath may show an extreme hæmorrhagic exudation. Abundant hæmorrhage is also often found in the glands and filling up their ducts.

The membrane usually extends over the mouths of the mucous glands without passing into them. In some cases, on the other hand, it passes directly into the mucous glands, the epithelial lining of which is necrotic. The membrana propria in most places is intact and forms a sharp line of separation from the membrane above and the tissue beneath. A few leucocytes can be seen passing through it. In their passage through it they assume the small attenuated shapes which they show when migrating in the cornea and in passing through the wall of a vessel. In most cases they do not seem to pass through in a straight line, but in a rather irregular manner. Here and there along the surface just below the membrana propria there are small areas representing hyaline fibrinoid metamorphoses of the connective tissue. (Plate XVI., Fig. 2.) Usually they are of very small extent and opposite a point where the fibrin is adherent to the membrane. In many of these places the same change can be seen in the membrana propria. This becomes thinner and denser; often it seems to split or spaces appear in it, and it assumes with the iron hæmatoxylin the dark fibrin stain. Where the fibrin is adherent to the membrana propria it often spreads out like a foot stalk, and becomes directly continuous with the fibrinoid metamorphosed membrane and tissue. The fibrinoid

tissue is distinctly reticular. In a few of the specimens examined this change in the tissue was much more marked. A hyaline fibrinoid and fibrinous network was formed just beneath the membrana propria and seemed to be continuous with the membrane over it. Close examination was necessary to distinguish the thin fibrinoid membrana propria which seemed to be a part of the reticulum. In some cases, however, the membrana propria was clearly absent; the reticulum in the tissue was directly continuous with the membrane. The fibrinoid change of the connective tissue is beautifully shown by Mallory's connective tissue stain. This shows also that the first change in the connective tissue consists in swelling of the fibres. They become homogeneous and more refractive. The swollen tissue stains blue, but not so sharply as ordinary connective tissue, and gradually becomes reticular. Later the reticulum takes the reddish-yellow fibrin stain, either wholly or in places. Portions of the reticulum or single fibres still staining blue can be traced into the fibrin bands.

In 9 cases there was a formation of membrane on the tongue due to an extension of the membrane from the tonsils. In most cases the epithelium had entirely disappeared and the membrane was composed of fibrin without any hyaline. The membrane was usually thicker on the apices of the papillæ than elsewhere. In one case every papilla in the section was covered by a cap of fibrin (Plate XVII., Fig. 1), and between there was no membrane.

In the œsophagus, in which membrane was found in 12 cases, its formation could be studied better than elsewhere. Macroscopically there were small losses of substance consisting simply of erosions of the epithelium extending longitudinally. These were covered with a thin adherent membrane. Between these erosions there were areas where the surface was thickened and covered with a grayish necrotic-looking mass, alternating with areas of normal mucous membrane all extending longitudinally. On microscopic examination small foci were found in the apparently normal mucous membrane which marked the beginning of the lesions. Here the

cells were swollen, the interior of the cells pale, vacuolated, the nuclei apparently lying in spaces. The contact edges of the cells were more prominent, forming a pale reticulum. Certain of the cells, instead of undergoing this vacuolation or œdema, were converted into refractive hyaline masses. No fibrin was found in these places.

The edges of the erosions were sharply cut. At the edge of the erosions the epithelium was undermined and showed an extraordinary degree of the nuclear proliferation by direct division. In some places there was little at the edge save the mass of partly broken down vesicular nuclei. The adjoining nuclei showed the peripheral arrangement of chromatin and segmentation. In places bare of epithelium there was a small amount of membrane on the surface, and a slight extension of the fibrin into the tissue beneath. In the place where macroscopically there was evident membrane, this was found microscopically to consist of a fibrinous reticulum with here and there small bits of thicker hyaline membrane. In one specimen there was very evident participation of the epithelium in the formation of the membrane. The upper layers of cells seemed to be lost or converted into detritus. Lower down the single epithelial cells were separated, and between them was an irregular fibrinous reticulum. The cells themselves were refractive and hyaline, and around the periphery of many of them was a thin line which gave the fibrin stain. In many places there were vesicles containing masses of such altered cells, together with much nuclear detritus. In the cells which were most altered no nuclei could be distinguished. Where the change was less advanced the nuclei were swollen and either disintegrated to a mass of detritus or segmenting.

The tissue beneath was intensely hyperæmic. Around many of the blood-vessels there was hæmorrhage and infiltration with polymorphonuclear cells and lymphocytes. In the membrane there were numerous infiltrating cells, both lymphocytes and polynuclear leucocytes, principally the former.

In the comparatively intact mucous membrane near the

erosions and the membrane formation there were numerous lymphocytes between the epithelial cells. While the membrane was chiefly fibrinous, hyaline areas were found which extended from the membrane into the tissue beneath. The hyaline membrane had only in places the definite reticulum which was so prominent in the tonsils.

The membrane in the pharynx and palate was in general similar to that described on the tonsils. The soft palate and uvula were particularly good for the study of the membrane. Both the fibrinous and hyaline membranes were found, more generally the former. Small amounts of mucin were occasionally present in the membrane.

Membrane was found on the epiglottis in 60 cases, and in 2 this was the only situation which showed it. Usually it was extensive, covering both sides of the epiglottis as a dense grayish or black mass. Hyaline membrane was found, but not so frequently as in the tonsils. The membrane usually consisted of a fibrinous reticulum, the meshes of which varied in size and which ultimately was connected with a fine fibrinous exudation in the tissue.

The changes in the lymphoid tissue of the tonsils will be spoken of in connection with the changes in the lymph nodes.

There was frequently considerable hæmorrhage in the tissue beneath the membrane. (Plate XIX., Fig. 1.) In many cases large numbers of red corpuscles were found in the membrane. The dark, almost black color of the membrane often found was due to the presence of blood. In all cases the blood-vessels beneath the membrane were more or less affected and the character of the changes in them did not appear to be always the same. Usually immediately beneath the membrane the vessels were occluded by a mass of very much the same character as the membrane. In some the material was obviously fibrin, in others it had the same character as the hyaline membrane. The entire wall of the vessel was swollen, hyaline, and stained with the fibrin stain. The vessels were often surrounded by a fibrinous or hyaline membrane connected with the membrane

bove, and were often so altered that their character could not be ascertained. The change seemed to affect both arteries, veins, and capillaries; the latter were represented by dark lines of hyaline. The changes preceding this complete degeneration could often be traced in the small arteries. In these, small masses of homogeneous material giving the fibrin stain appeared in the wall. This material appeared first between the muscle cells of the media, and afterwards the cells were either changed into or covered up by it. (Plate XVIII., Figs. 3 and 4.) The whole change presented a marked similarity to amyloid infiltration of blood-vessels. It appeared to be a hyaline fibrinoid metamorphosis of the same character as that described in the connective tissue. The hyaline material within the vessels sometimes was in the form of a reticulum, at others in large irregular clumps adhering to the wall. In other cases the change affected the internal elastic lamina, which became swollen and hyaline. The most marked changes were found in the vessels nearest the membrane and were less intense in the vessels deeper down. The change was most marked in the epiglottis and tonsils. It was less marked in the œsophagus and trachea. The vessels showing the slightest degree of this alteration were filled with unaltered red corpuscles and an apparently normal circulation was taking place in them. Thrombi were very frequently found in the underlying veins.

Another marked change in the vessels was the proliferation of the nuclei in the small veins, but this was so much more marked in the veins in the lymphatic tissues that it will be more fully described in connection with them.

Both the superficial and deep lymphatic vessels were dilated. They contained a finely granular coagulated material and very few cells. (Plate XIX., Fig. 1.) Their nuclei showed no change. Where the tissue was most altered, immediately beneath the membrane, the lymphatics could not be recognized with certainty, and it is possible that some of the hyaline vessels in the tissue may have been lymphatics. All observers have particularly called attention to a general

cellular infiltration of the tissue below and in the vicinity of the membrane. Under normal conditions there are great numbers of lymphoid cells in the mucous membrane of the throat, not only in the lymphoid tissue itself, but as a more diffuse infiltration. This general infiltration was in some cases markedly increased, in others not. The cells were almost exclusively lymphoid and plasma cells. Polymorphonuclear leucocytes were found as a rule only in connection with necrotic tissue, either in the necrotic tissue or in the tissue around it.

Marked changes were found in the mucous glands of the tissue. These varied from congestion with slight degeneration to complete necrosis. The slightest form of degeneration consisted in swelling and œdema of the cells. The lumen of the alveolus of the gland was occluded by the projection of the swollen and vacuolated cells. Brightly stained granules were often contained in the vacuoles. The vacuoles were most marked in the portion of the cell bordering the lumen. Hyaline globules similar to those found in the epithelium of the kidney were found in the single cells, and in some cases the entire mass of cells was converted into hyaline, in which nuclear fragments were found. Not infrequently the cells contained small round masses similar in appearance to certain of the inclusions in carcinoma cells. In the most marked degeneration entire alveoli were converted into granular masses containing nuclear detritus. Polynuclear leucocytes in various stages of degeneration were found in the tissue. The interstitial tissue of the glands was variously affected. In the slightest cases the tissue was œdematous with more or less cellular infiltration. In some cases there was extensive hæmorrhage in the gland and extending into the surrounding tissue. This degeneration of the glands was most marked in those near the surface. It extended, however, into the deeper portions and was more marked in the surrounding tissue. This glandular degeneration accounts to us to account for the very small amount of mucus found in connection with the membrane. The reason why the membrane is so easily retracted from the trachea is that it is elevated by the mucous

from the glands beneath. We have never seen any evidence of this. The glands are so degenerated as to seem incapable of secretion.

In most of the cases there were evident alterations in the striated muscles of the pharynx. They were most marked in the muscle nearest the membrane and became progressively less further down. There was general œdema; the muscle bundles and the individual fibres were separated from one another. In many cases there was hæmorrhage, fibrin, and infiltration with leucocytes.

The first change which took place in the muscle fibre was the disappearance of the fibrillæ; the fibre became converted into a swollen, homogeneous, refractive mass. This change seemed most often to begin in the centre of the fibre. Cross-sections often showed fibres with a comparatively homogeneous centre surrounded by intact fibrillæ. In the swollen fibres there appeared to be a system of small vacuoles giving to the cross-section the appearance of a very fine reticulum. In the more altered fibres this was lost and the homogeneous material in some cases showed fine fracture lines radiating from the centre, or it was broken up into a number of small masses. In the most altered fibres the nuclei either had disappeared or were fragmented. Occasionally degenerated nuclei in all stages of direct division were found. Where the fibres were most altered and broken down they often contained numbers of leucocytes. Varying degrees of hyaline degeneration were found in the vessels.

Distinct ulceration involving a greater or less degree of tissue was found in 12 cases. The ulceration involved the tonsils 5 times, larynx 3, trachea 2, pharynx 1, epiglottis 1. All of these were severe cases and all of them were intubed. In the tonsils the ulcers were produced by extensive necrosis extending from the membrane into the tissue. They were foul and ragged; the necrosis extended into the tissue from the sides of the ulcer. Those in the pharynx and epiglottis were of the same character as in the tonsils, though not so extensive. Those in the air passages were clearly due to

the influence of the intubation tube. Those in the trachea were less marked.

One case was in a child who died on the sixteenth day of the disease, and who was intubed on admission into the hospital one week after the disease appeared. In the trachea, which contained only shreds of membrane, there were several small clean-cut ulcers extending the sides there was a small amount of necrotic tissue. Large numbers of cocci in coccus form. They extended into the pus cells. The necrotic tissue was found both in the pus cells, and in the adjoining tissue and evidences of repair. An ulcer was shown in the trachea of a second case, a day and which also was intubed. Extensive membrane in the trachea. Diphtheria bacilli and cocci on the membrane. In one place in the section

There was a sharply circumscribed necrosis at this point, 3 mm. in width, and extending to the cartilage. On the surface there were some masses of diphtheria bacilli and but few other organisms. In the interior the necrotic tissue was filled with masses of cocci so numerous that the whole tissue stained blue with the bacteria stain. The organisms extended for some distance into the tissue beyond the necrosis. The necrotic tissue showed but little evidence of purulent infiltration and there were but few pus cells in the adjoining tissue. The ulceration was evidently due to the casting off of the necrotic tissue. The necrosis was due to the pressure of the laryngeal tube.

In the earlier cases in which there was a definite membrane the diphtheria bacilli were found almost without exception in the histological preparations. In the later cases they generally were missed, although in some instances they were present in large numbers. They were found chiefly in clumps of varying size, on the surface of the membrane. This was particularly the case in the trachea, but was not

so obvious in the tonsils. The clumps of bacilli varied in size from small groups in which all the bacilli could be counted to large masses of the micro-organisms filling the entire field of an immersion. In the vicinity of the large masses very small groups of bacilli were found. Even when growing on the surface the bacilli were in the necrotic tissue and fibrin and not in free masses. In a few specimens groups were found deep down in the membrane, but these groups usually did not stain so brightly as those on the surface. They were often found on the surface in what could be recognized as degenerated epithelial cells, filling them up, and small groups were found corresponding in size and shape to such cells. In three cases in which the hyaline membrane with thick reticulum was very evident the bacilli were found growing on the surface in this membrane, forming with a low power a blue mass having the form of the reticulum. With higher power the single bacilli could be recognized in the reticulum, in some cases filling this up, or single ones were seen on the surface. Occasionally they were found scattered in considerable numbers in the depths of the membrane enclosed in polynuclear leucocytes. In but one case of extensive membrane formation in the pharynx were they found below the surface, and here they were enclosed within polynuclear leucocytes.

In no case were the bacilli found in connection with the epithelial degenerations, which probably should be regarded as the initial lesions in the membrane formation. This was very evident in the œsophagus, where apparently the very earliest lesions were found. In one section, which showed only superficial desquamation of the epithelium with vacuolation and direct nuclear proliferation, close examination failed to show a single bacillus, while numbers of them were found in an adjoining piece of membrane.

In many cases where the bacilli were most numerous they were growing on the membrane in pure culture; no other organisms seemed to be mixed with them. In no case were other organisms found mixed with the bacilli in the single clumps. As a general rule, where the bacilli were most

prominent the other organisms were least evident. Of the other organisms, cocci were the most numerous. In one section of the epiglottis small groups of very large brightly staining cocci similar in appearance to the large cocci so often found in throat cultures were found. Cocci in diplococcus form often were found enclosed in pus cells. Streptococci were more common in the tonsils. In one case in which there were extensive necroses extending from the crypts into the tissue, large masses of streptococci were found in the necrotic tissue. Occasionally the masses on the surface were filled with masses of c a dark rim around the edges. The membrane masses on the surface were in two cases found d by a leptothrix, forming a dense mass of n long threads parallel to one another.

It was interesting to see that the membrane and the necrotic tissue in connection with it could be invaded by fungi. In a section of the epiglottis which contained membrane with bacilli, there was an area in which the membrane was broken down into a mass of detritus. In this the mycelium of a fungus was found with the threads growing perpendicular to the surface. The growth extended down to the tissue beneath, but did not invade it. A similar condition was found in another case on the surface of the tonsil, and here the threads of the mycelium extended into the tissue and were surrounded by cells. That such a growth of a fungus can extend deeply into the tissue was shown in a section of the tonsil in one case. In the tonsil there was a slight formation of membrane on the surface containing diphtheria bacilli and cocci. Deeper down in the tissue and close to the crypt were a number of giant cells arranged around filaments of the mycelium of a fungus. The filaments stained imperfectly and probably were degenerated.

Investigated histologically was one of membrane of the ear following diphtheritic otitis media with perforation of the drum; the infection of the ear took place from the discharge running down over it.

B. C. H., '97. 371. Child two years old.

Posterior third of tongue is covered with a dirty greenish-gray membrane which extends out over the tonsils, both of which show losses of substance and are covered by dirty gray necrotic material. The membrane extends backwards over the pharynx, epiglottis, and into the larynx to a point just below the vocal cords. The membrane is extremely dirty and foul smelling, and can be removed with slight force, leaving a granular surface beneath. Trachea and bronchi normal.

Stomach. — At the junction of the œsophagus and stomach there are 3 small losses of substance covered with a thin grayish membrane. These areas are about the size of half a pea. Around them the mucous membrane is hyperæmic and covered with mucus.

Nose. — The membrane extends from the pharynx up into the posterior nares, which are filled with thick, firm, greenish, foul-smelling membrane which can be easily removed.

The left antrum of Highmore contains a grayish-white fluid, and from its walls small pieces of false membrane can be stripped off. Right antrum shows a similar condition.

Right external ear. — The entire lower and posterior portions of the ear are reddened and covered irregularly with a thin whitish false membrane. Behind the ear is a fissure 1.5 cm. long, covered with membrane of same character. For an area of 2 to 3 cm., all around the ear, the skin is reddened, and shows a slight serous exudate and desquamation of the epithelium. The external meatus contains a small amount of cloudy fluid. The middle ear and mastoid cells are filled with a dirty greenish-yellow purulent fluid, of extremely foul odor. The membrana tympani is ruptured. Cultures from membrane on external ear show diphtheria bacilli and the staphylococcus aureus; from right middle ear diphtheria bacilli, the streptococcus, and the pneumococcus.

Microscopical examination of the ear showed on the surface a mass composed of blood and dried exudation, and beneath this a fibrinous reticulum enclosing pus cells. In places this mass lay upon the epithelium, which was comparatively intact, although the horny cells were swollen and separated. In other places the epithelium was entirely removed, or only the lower layers were preserved. In many of these places there was the same hyaline degeneration of cells

and fibrin formation between them which has been described in the œsophagus. The inflammation was essentially hæmorrhagic. (Plate XVIII., Fig. 1.) The blood vessels were distended, there was hæmorrhage around them, and the entire tissue contained great numbers of blood corpuscles. Blood corpuscles were found in the membrane on the surface, and in the epithelium. Pus cells were present in comparatively small numbers. There was extension of the tissue beneath, which was continuous on the surface. This particularly involved the appendages, and extended into the glands. The sebaceous glands were filled with a mass of reticular fibrin, and the cells were filled with fragmented nuclei. In the deeper layers there was a fibrinous exudation, œdema, and degenerated fibres. There were numerous cells in the necrotic tissue small masses of cells stained very imperfectly.

We have taken from the clinical records the following excerpts relating to other skin lesions:

Subcutaneous ecchymoses occurred in 2 cases. In 1, a child aged four and one-half years, they appeared on the fourth day and were quite generally distributed; in the other, aged six years, they were limited to the lower extremities.

Erythema multiforme appeared on the third day in a case aged fifteen years.

A vesicular eruption with slightly raised borders appeared in a child four years old. It involved all parts of the body. The vesicles first appeared on the first day and increased in number up to the third day.

We have found in the literature the following references to diphtheria of external parts:

Prescott found diphtheria bacilli in the throat treated by a poultice applied to enlarged lymphatic glands. Cultures from the throat and nose were negative. Diphtheritic conjunctivitis have been reported by Elschig, Kalisko, Paltauf, Escherich, a

reports a case in which diphtheria bacilli were found in inflammatory tissue around the anus. Dr. Abner Post has also found a diphtheritic inflammation of the skin around the anus with diphtheria bacilli in the cultures, in a case in which no bacilli were present in the throat and nose. (Case not previously reported.) Wright reported a case of diphtheritic conjunctivitis due to diphtheria bacilli; 7 cases of ulcers and abrasions of various parts of the body in which the bacilli were found; and also 1 case of fistula in ano. Park reported 2 cases of wound of a finger in which diphtheria bacilli were found; McCollom 2 cases of diphtheria of penis; Brunner 1 case in which diphtheria bacilli were found in a phlegmon of the scrotum, and 3 cases in which the bacilli were found in various inflammatory processes of the fingers; Flexner and Pease 2 cases of primary diphtheria of the lips and gums. There are quite a number of reports of diphtheria of the female genitalia. Maultain, Nisot, Longyear, Stahl, Bumm, report cases of diphtheria of the uterus developing in the puerperal period; Williams and Müller cases of diphtheria of vagina and external genitalia.

Summary.

We have never found the diphtheria bacilli growing in the living tissue, or in connection with those degenerative lesions in the epithelium which can be regarded as the primary lesions of the disease. They were found in the necrotic tissue and in the exudation, usually only in the latter. In a very few cases the bacilli were found enclosed in pus and in necrotic epithelial cells. They were nearly always found in clumps and masses. The masses found deep down in the membrane probably do not represent a downward growth in this, but have been covered up by a further formation of membrane on the surface. The diphtheria bacillus shows in its growth an affinity for solid structures, and is found rather on the reticulum than in the spaces between. It seems most probable to us that the beginning of the lesions is due to the toxic action of bacilli possibly growing in the fluids of the mouth

or throat. When necrosis is once produced the necrotic tissue forms a suitable culture medium. Usually other organisms, particularly the pyogenic cocci, are found associated with it, though not intimately. The membrane and necrotic tissue may also be invaded by fungi.

The membrane formation is due to a combination of processes. It seems probable that the first step in its production is degeneration and necrosis of the epithelium, often preceded by active proliferation of the nuclei of the cells by direct division. The cells may either break up into detritus, with fragmentation of the nuclei, or they may become changed into refractive hyaline masses. An inflammatory exudation rich in fibrin factors comes from the tissue below, and fibrin is formed when this comes in contact with the necrotic epithelium. The fibrin in part is formed into a reticulum around exudation cells and degenerated epithelium, in part it combines with the hyaline degenerated cells to form a hyaline membrane. It is probable that a hyaline membrane may be formed without the exudation; in this case the network of the membrane represents the edges of the cells, and the spaces the former nuclei. The hyaline membrane is most often formed on those surfaces which are covered with epithelium having several layers of cells. It may be formed by a hyaline degeneration of exudation cells; in this case the spaces in the meshwork are smaller. It is probable that the fibrinous membrane is formed both on the surfaces and in the tissue. The fibrin is first formed around cells which afterwards disappear. In the trachea the fibrinous membrane often has a definite structure. The membrane may disintegrate and be broken up into a mass of detritus (the process commences on the surface), or it may be cast off as a whole by being elevated by an exudation beneath. Very thick masses of membrane may be formed by the constant addition of fibrinous exudation. The membrane is never formed primarily on an intact epithelial surface, but it may extend over it. Nothing is to be gained by making an anatomical distinction between a croupous and a diphtheritic membrane. There is nothing specific in the membrane formation in diphtheria.

We have found typical hyaline and fibrinous membranes in cysts of the ovary in the formation of which bacteria played no part.

The membrane formation is accompanied by changes in the tissue beneath, which represent a combination of degeneration and exudation. The connective tissue and blood vessels undergo a hyaline fibrinoid degeneration very similar to the degeneration of the epithelium. Necrosis may extend deeply into the tissue, but there is little tendency to deep ulceration or abscess formation. The degeneration in the mucous glands of the tissue is so pronounced as to be almost specific. Marked degeneration of the epithelium of the glands may be found without any change in the surrounding tissue. The changes in the blood vessels, though so pronounced in diphtheria, are not specific. We have frequently found changes in all respects similar in the walls of abscesses and ulcers. The extent of the necrosis in the primary lesions is greater than is found in the action of any other bacteria.

HEART.

The changes produced in the heart in diphtheria have received more attention than have any of the other visceral lesions. Most of these investigations were undertaken with the view of finding in pathological conditions in the heart an explanation of the clinical evidences of impaired cardiac action. The earlier investigators regarded the presence of clots (there was no distinction made between these and thrombi) as a sufficient explanation of the clinical conditions. Apart from the work of Mosler, who described degenerative conditions in the heart muscle in diphtheria, the first careful anatomical investigation of the heart in diphtheria was by Hayem. He described changes in the muscular tissue consisting of granular and fatty degeneration, and of changes in the vessels and in the interstitial tissue. He was undoubtedly the first to describe the acute interstitial myocarditis. He says the muscular fibres atrophy, there is an increase in the connective tissue, and new elements appear between the

fibres. He particularly described irregular round or oval forms which have one and sometimes two nuclei. There were also smaller cells supposed to be new muscular large cells. Shortly before this Huchard investigated the heart work did not add to our knowledge. Rosenbach described granular degeneration of the muscular fibres and cellular tissue. There was proliferative fibres following the degeneration which took the place of the interstitial infiltration was most common, the degeneration being described by Hirschfeld found acute interstitial myocarditis of diphtheria in which death was due to fatty degeneration of the fibres, their nuclei, and cellular infiltration. In two of the three cases he described acute interstitial myocarditis, essential pathological condition of paralysis. The interstitial changes in the degeneration of the fibres, but was not the case he examined the vagus nerve. Unruh describes myocarditis as changes in the cardiac muscle which failure is due to changes in the conduction system and the definite paralysis of the nerves of the heart and the other nerves later. The changes show that the cause is due to the changes described in both typhoid and endarteritis in the coronary arteries, degeneration of the myocardium. Huguenin found granular degeneration of the muscular fibres, increase of connective tissue, the nuclei, and small hæmorrhages.

matous and interstitial myocarditis, and of proliferating endarteritis. He found the pneumogastric nerve and medulla normal. Oertel found degeneration and foci of interstitial infiltration. There was a general increase both in the size and number of the nuclei of the muscle fibres. The nuclei often were several times their normal length and were irregular in outline. Appearances indicating direct division were seen, but this was regarded as indicating degeneration. The greatest change found by Oertel in one of the three cases examined was immediately beneath the endocardium adjacent to the coronary arteries. The enlargement of the nuclei of the muscular fibres had previously been described by Ehrlich in a case of pernicious anæmia, and was regarded by him as a degenerative condition; he believed that the nuclei enlarged to take the place of the diminished muscular fibres. Schemm describes fatty and granular degeneration of the heart muscle fibres, with swelling and increase of the nuclei, and a slight hyaline degeneration and atrophy. The connective tissue is often rich in cells, and in one case he found blood extravasations. Savigne found the muscular fibres variously altered and embryonic infiltration of the interstitial tissue with round and lymphoid cells. He thinks the interstitial change does not necessarily lead to increase of the connective tissue. Rabot and Philippe describe granular degeneration of the muscular fibres of the heart, with a slight increase in the size of the nuclei, and with small areas of inflammatory infiltration. They found no changes either in the peripheral nerves or in the central nervous system, and conclude that the essential process in the heart is an interstitial myocarditis. By far the most important article on the condition of the heart in diphtheria is that by Romberg. He studied sections made from a number of different places in the heart in eight cases of diphtheria and found great variation in the extent of the lesions. A section cut from one part of the heart may be normal, while one from another part may show extensive lesions. There were small foci of leucocytic infiltration around the smaller coronary arteries, while the larger were intact. Degeneration of the muscle

fibres. He particularly describes large granular cells of irregular round or oval form which lie between the fibres, and have one and sometimes two nuclei with evident nucleoli. There were also smaller cells analogous to leucocytes. He supposed that new muscular fibres were formed from the large cells. Shortly before the work of Hayem, Desnos and Huchard investigated the heart in cases of smallpox, but their work did not add to our knowledge of the pathological anatomy. Rosenbach described granular and waxy degeneration of the muscular fibres and cellular infiltration of the interstitial tissue. There was proliferation of the nuclei of the muscular fibres following the degeneration, and large cells were produced which took the place of the muscular fibres. The interstitial infiltration was most marked beneath the pericardium, the degeneration beneath the endocardium. Birch-Hirschfeld found acute interstitial myocarditis in two cases of diphtheria in which death took place suddenly. Leyden found fatty degeneration of the muscular fibres, increase of their nuclei, and cellular infiltration around the blood vessels. In two of the three cases he investigated there were areas of acute interstitial myocarditis, and he regards this as the essential pathological condition and the cause of the heart paralysis. The interstitial change was accompanied by degeneration of the fibres, but was not dependent upon it. In one case he examined the vagus nerve and found it normal. Unruh describes myocarditis in localized areas and fatty changes in the cardiac muscle. He does not think the heart failure is due to changes in the nerves, because it is an early symptom and the definite paralyses appear later. He asks why the nerves of the heart should be affected so early and the other nerves later. The dilatation of the heart also shows that the cause is due to changes in the muscle. Martin described in both typhoid fever and diphtheria acute endarteritis in the coronary arteries, and regarded the degeneration of the myocardium as secondary to this lesion. Huguenin found granular and hyaline degeneration of the muscle fibres, increase of connective tissue, much increase of the nuclei, and small hæmorrhages. He speaks of parenchy-

matous and interstitial myocarditis, and of proliferating endarteritis. He found the pneumogastric nerve and medulla normal. Oertel found degeneration and foci of interstitial infiltration. There was a general increase both in the size and number of the nuclei of the muscle fibres. The nuclei often were several times their normal length and were irregular in outline. Appearances indicating direct division were seen, but this was regarded as indicating degeneration. The greatest change found by Oertel in one of the three cases examined was immediately beneath the endocardium adjacent to the coronary arteries. The enlargement of the nuclei of the muscular fibres had previously been described by Ehrlich in a case of pernicious anæmia, and was regarded by him as a degenerative condition; he believed that the nuclei enlarged to take the place of the diminished muscular fibres. Schemm describes fatty and granular degeneration of the heart muscle fibres, with swelling and increase of the nuclei, and a slight hyaline degeneration and atrophy. The connective tissue is often rich in cells, and in one case he found blood extravasations. Savigne found the muscular fibres variously altered and embryonic infiltration of the interstitial tissue with round and lymphoid cells. He thinks the interstitial change does not necessarily lead to increase of the connective tissue. Rabot and Philippe describe granular degeneration of the muscular fibres of the heart, with a slight increase in the size of the nuclei, and with small areas of inflammatory infiltration. They found no changes either in the peripheral nerves or in the central nervous system, and conclude that the essential process in the heart is an interstitial myocarditis. By far the most important article on the condition of the heart in diphtheria is that by Romberg. He studied sections made from a number of different places in the heart in eight cases of diphtheria and found great variation in the extent of the lesions. A section cut from one part of the heart may be normal, while one from another part may show extensive lesions. There were small foci of leucocytic infiltration around the smaller coronary arteries, while the larger were intact. Degeneration of the muscle

fibres was the most marked lesion. The fibres most degenerated had no nuclei. He also describes a peculiar vacuole formation in the centre of the fibre. Krehl had previously described this condition and regarded the vacuoles as due to fat.¹ He found a marked change in the nuclei of the muscular fibres consisting of hypertrophy with an accompanying vesicular condition which he regarded as degeneration and not indicating nuclear proliferation. The inner and outer portions of the myocardium were most subject to degeneration. Interstitial changes were found in all cases. They were in foci and were more common beneath the pericardium. The interstitial change consisted of cellular infiltration around the vessels and between the fibres. Most of the interstitial cells were leucocytes, but among them were large cells similar to those described by Hayem. There was no connection between the degeneration of the muscle and the interstitial infiltration. He thinks the large cells may be myoplastic, but he has never seen striation in them. The interstitial foci may heal, suppurate, or lead to areas of fibrous myocarditis. There was pericarditis in 5 of the 8 cases and endocarditis in 3. Arnheim examined the heart in 8 cases and found degeneration in 3. Hesse examined the heart in 29 cases and found but little in the macroscopic examination save dilatation of the apices of the ventricles in prolonged cases. In one case of 28 days' duration both ventricles were dilated and hypertrophied. The parenchymatous changes were not marked under 3 days and were more evident in the right than the left side. In 25 of the 29 cases there was some interstitial myocarditis, and in 4 it was pronounced. It was noticeable in the first week of the disease, but was more marked in the third and fourth. The left ventricle was most often the seat of the interstitial change. The cells in the interstitial tissue were leucocytes, and their presence was due to changes in the vessels produced by the toxin in consequence of which they become more penetrable. He concludes that the sudden death in diphtheria is due to heart

¹ It is possible that the condition of vacuolation described by Romberg did not refer to the actual fat vacuoles, but to the disappearance of the contractile elements in the centre of the fibre, a degenerative condition often met with.

failure brought about by the action of toxins on the heart. Preisz in one case of death from heart failure found that the muscular fibres of the heart had lost their striations and were granular, while the nerve cells stained by Nissl's method showed no change. Vincent in a case of sudden death due to diphtheria found no change in the muscle save loss of striation of the muscular fibres. There was some increase in the nuclei of the sarcolemma, and the connective tissue cells were increased about the blood vessels. The vessels of the heart were dilated, but there was no cellular infiltration or hæmorrhage, and no changes in the nerve cells. The myelin sheaths of the nerve fibres in the pneumogastric nerve were thickened in places, but there was no marked degeneration. The sympathetic nerve was normal, but in the lower cervical sympathetic ganglion some of the cells showed granular degeneration. In the cardiac plexus he found marked changes. There was intense parenchymatous degeneration and absence of the axis cylinders. The capillaries were dilated and the nerve cells were granular, vacuolated, and in some there was loss of the nucleus and nucleolus. Schamschin found in addition to the degeneration of the muscular fibres, which was more pronounced in the papillary muscles, fatty degeneration of the walls of the small blood vessels and of the cells contained in them. The cells in the interstitial tissue he regarded as emigrated leucocytes. Papkow examined the hearts of children from one and a half to nine years old who had died of diphtheria from the third to the fourth day, without treatment by antitoxin. In all cases there was extensive fragmentation of the muscle, with white and red blood corpuscles between the fragments. The cause of the fragmentation was the swelling and destruction of the cement substance. He thinks this is an early change and he ascribes it to the cardiac weakness which is often seen as early as the third day. The waxy degeneration and interstitial changes belong to a later period of the disease. Scagliosi found chiefly degeneration of the muscle affecting groups of fibres. He did not find that interstitial processes play any decided part in the alterations. There is fatty de-

were treated in this way for five months, the consistency of the myocardium was increased and white patches found in it. These proved to be areas of fibrous myocarditis which followed the acute degeneration.

In addition to routine examination of fresh sections at the autopsy to determine fatty degeneration a more complete examination was made in 60 cases. The same methods of hardening and staining were used as in the case of the other tissues. The examinations of the heart are incomplete in that the condition of the cardiac ganglia and nerves was not investigated, nor was a sufficient number of pieces from different parts of the heart examined. As a rule pieces were taken for examination from the interventricular septum and from the wall of the left ventricle near the aorta.

Fatty degeneration of the muscular fibres varying in extent and degree was found in 36 of the 60 cases. The presence of fat was determined in most cases by fresh examination at the autopsy. In thin sections of tissues hardened in Zenker's fluid it is easy to determine any considerable degree of this degeneration (Plate XXI., Fig. 1) by the large vacuoles left in the fibres after the fat is dissolved out, but the minor degrees will escape observation. It is probable that the number of cases given is below the actual number, for fresh examinations were made in only 40 of the 60 cases, and it might have been missed in the examination of the hardened sections. Of the 40 cases in which fresh examinations were made it was present in 29. In all there were fresh examinations made in 67 cases, this including the 40 cases in which hardened sections were examined as well, and in 46 of the 67 cases fat was found. The extent of the degeneration varied greatly. In some cases it was denoted only by the fine longitudinal rows of dots in the muscular fibres, in others there seemed to be but little of the substance of the fibre remaining. The fatty degeneration was in some cases the only change recognizable in the muscular fibres, but it was constantly found accompanying the more advanced forms of degeneration leading to necrosis and complete destruction of

the fibres. In the least marked cases it was diffuse; only single scattered fibres were affected. Cases were found, however, in which there were areas of marked degeneration, and between these areas occurred single degenerated fibres. It was always more marked in the vicinity of the endocardium than elsewhere. There was but little relation between the duration of the disease and fatty degeneration; it was found in cases of short and of long duration. It was generally the only lesion of the myocardium in the cases of great severity which died shortly after entering the hospital.

Segmentation of the myocardium, separation of the fibres along the line of juncture, without other serious lesion, was not found in a single case. There were numerous cases of fragmentation and rupture of the muscle fibres in the degenerated areas, and this condition was sometimes accompanied by slight degree of segmentation. It seemed to us that this was probably due to the good preservation of the tissue and the care exercised in making the sections. In the routine examinations of the myocardium made at the City Hospital we have been surprised at the infrequency of this lesion, which, according to the observations of some authors, should be regarded as one of the most common lesions of the heart.

In 13 cases very much more (to complete destruction of the (Plate XXI., Fig. 4.) This was degeneration, and in some cases This degeneration affected all the contractile elements, the protoplasmic some cases the disappearance of the most obvious lesion. In hæmatoxylin, which brings out muscle fibres, cross-sections showed were generally swollen, and in some appeared to a greater or less extent. In cases the degeneration took place. Fibres were frequently found in the margin which was normal. In some elements seemed to have disappeared

by granular material; in others the rods were swollen and fused together. Many of the fibres contained large rather irregular vacuoles which could be distinguished from the fat vacuoles by their large size and irregularity of shape. A further form of degeneration consisted in the complete destruction of the fibrillæ with the formation of large irregular hyaline masses, which stained with hæmatoxylin. Cross-sections showed entire fibres converted into a hyaline mass, which often showed fine lines of fracture radiating from the centre. Longitudinal section of fibres which were least degenerated showed increase in the protoplasm around the nucleus. The protoplasm was coarsely granular, and contained hyaline. In the least marked cases only single scattered fibres were degenerated, and surrounded by fibres which were unchanged. On longitudinal section, the degenerated muscle cell frequently adjoined a normal cell which showed striation. In one case almost every fibre in a section from the interventricular septum was affected; but the degeneration was not extreme, and affected only the centre of each fibre. Where the degeneration was extreme, it was both general and focal; areas were found in which almost every fibre was destroyed. In one case it was estimated that at least one-third of the total substance of the heart was destroyed. There was a definite relation between this intense degeneration and the duration of the disease. It was found only in the later stages. The average duration of the 13 cases was 15 days. The degeneration was present in slight degree in 1 case of 6 days' duration, and was best marked in 2 cases, 1 of 20 and 1 of 13 days' duration. It was also extensive in 1 case of 42 days' duration. The degeneration was always more intense on the endocardial side than elsewhere, and in 1 case was limited to the fibres of the papillary muscles. Various changes in the nuclei were almost universally found accompanying the degeneration of the fibre. The most common condition observed in the nucleus was swelling and increased vacuolation. The degenerated nucleus was vesicular, and the edge often remarkably irregular. Not infrequently two or even a series of such nuclei were found together. This evi-

dent increase in the nuclei was due to direct division, nuclear figures never being found. The constriction of the nucleus, and the changes in the chromatin indicative of direct division, were often seen. In addition to these changes consisting of vesicular swelling and direct division, the changes described by Romberg were frequently observed, particularly in the least altered fibres of degenerated areas. The nuclei stained intensely and homogeneously, and were often enormously enlarged, so that they were several times the size of the normal. No evidence of either direct or indirect division was seen in these degenerated nuclei.

In several of the earlier cases there was oedema of the tissue. Not only were the muscle masses wider, but the single fibres separated from one another. In the case in which the oedema was marked there was an increase in the width of the fibres which was probably due to the oedema.

Interstitial lesions consisting of cellular infiltration (XXII., Fig. 1) of the interstitial tissue with an actual increase in the tissue were found in several cases. We have not included in our series those cases in which polynuclear leucocytes were found between the degenerated fibres. Acute interstitial inflammation is focal, although in addition to the focal there may be some general increase in the interstitial tissue. It may or may not be associated with degeneration. Two forms may be distinguished, certain whether or not they can pass into one another. In one case small areas are found, often in the interstitium of muscular fibres, in which the interstitial septa and between the single fibres is dilated and filled with cells. Polynuclear leucocytes are among these cells. Nearly all observers have been struck by the large size and peculiar character of most of them; they are plasma cells of the same type as those found in the interstitial tissue of the kidney and other organs. Among them are lymphoid cells and cells found in connection with them. The num-

but they are rarely found in the compact masses in which they are seen in the kidneys. The foci are usually small and not sharply circumscribed; the cells extend from the focus into the surrounding tissue. Among the plasma and lymphoid cells larger cells with an epithelioid nucleus are sometimes found. Occasionally eosinophile cells are found in the foci, and in one case they were numerous. These cells had but a single nucleus and were similar to those found in the bone marrow. The number of these foci varies, but they are always more numerous close beneath the endocardium than elsewhere. In one case the interstitial change was confined to the papillary muscles. Cells similar to those in the interstitial tissue were found in the vessels in the foci. This form of interstitial myocarditis must be considered a rather rare heart complication in diphtheria. It is usually accompanied by degenerative changes in the muscle, but does not seem to be dependent on this, as the degeneration is not more marked in the interstitial foci than elsewhere. This form of interstitial myocarditis was found in but 6 cases. The average duration of the disease in these 6 cases was 10 days.

The other form of interstitial myocarditis was accompanied by and seemed clearly secondary to degeneration. The interstitial tissue, particularly in the septa, was dilated and infiltrated with large cells of an epithelioid character. There were a few lymphoid and plasma cells among them, but the epithelioid type predominated. In addition to the cellular infiltration there was in some cases considerable formation of connective tissue. This was particularly marked in one case of 42 days' duration. The average duration of the 14 cases was 17 days.

Changes in the vessels of the heart were not marked. In one case there was a recent thrombus in a branch of the coronary artery. In several cases the very rare condition of general capillary injection was found; death had evidently taken place in diastole and without further contraction after death. We do not remember of ever having seen this condition of general capillary injection of the heart in any other

case. The capillaries were very there was very little connective cases of marked degeneration a changes there was proliferation small veins and sinuses. The endo the same condition. There was the vicinity of the veins, but this No lesions were found in the arte uted to the acute infection. In o adult there was advanced endar nothing to do with the acute in

Heart thrombi were found in thrombi varied in size and situati ably in character. In two cases th puscles present; the mass of th blood platelets with separating ma Fig. 2.) The connective tissue s adapted to the demonstration of case was peculiar from the large cells included in the thrombus. mononuclear leucocytes, and amo of plasma cells and large and sma thelial lining of the endocardium the thrombi, and there was cellul the adjacent myocardium. In or auricle there was evident necros the necrotic tissue was infiltrated many of which were fragmented only case in which it was possib nection between the thrombi and it seemed probable that the thrc may have depended upon this a necrosis was not included in the found in the thrombi on microsc careful search was made for ther lation between the thrombi and th of the 8 cases there was not on tissue in the vicinity of the throm

was the seat of an interstitial myocarditis. Thrombi usually occurred in the cases of longer duration. The average duration of the 8 cases was 16 days. The most recent case was one of 6 days, and the longest one of 42 days.

In but three cases was there hæmorrhage into the myocardium, exclusive of the numerous cases in which small foci of hæmorrhage were found in both the peri- and endocardium. In two of the cases the hæmorrhagic foci were small and not numerous, and in one they were extensive. The hæmorrhages were not accompanied by extensive degeneration or by interstitial changes. The three cases in which they occurred were all of them of short duration.

In three cases there was pericarditis. In two of these the condition was acute, in one of long duration. In one of the acute cases the relation of the fibrinous exudation to the lining cells of the pericardium was beautifully shown. The exudation was on the surface of the endothelium, which was preserved and formed a line of proliferating cells. Here and there were small foci in which fibrin was found below the surface as well. In the more chronic case the fibrin had in great part disappeared or was converted into hyaline masses which were partly on the surface, partly enclosed by granulation tissue. The granulation tissue contained large numbers of plasma and lymphoid cells, among which were numerous large connective tissue forming cells. On the surface there was a line of these large cells. In this case the endothelial lining had almost entirely disappeared, and was represented only by the cells lining large cavities in the granulation tissue.

Summary.

Degeneration of the myocardium is one of the most common conditions found in diphtheria. The simplest form of this is fatty degeneration, which is found in the majority of all cases. This varies in extent, at times affecting the myocardium generally, at times occurring in foci. It may appear only in the form of fine granules at the junction of the cross and longitudinal striations, or in large globules which involve

the greater part of the substance fatty degeneration accompanies more advanced forms of degeneration complete destruction of the muscle.

of the sarcous elements, which become and converted into hyaline mass. vacuoles are formed in the cell, and their irregularity of shape from contraction and fracture of the degenerated found, but the segmentation or separation the line of junction does not take extent. Simple fatty degenerative cases of short duration, the more the more prolonged cases. The extensive as to account fully for the action. No bacteria are found in generation, but like most of the lesion the influences of the toxic substance.

Acute interstitial lesions of two sorts are focal collections of plasma in the tissue, which may be accompanied by myocardium, but are not dependent is analagous to acute interstitial condition the interstitial change comes from the cells of the tissue and is secondary to the muscle. It is probable that the formation of connective tissue and fibrous myocarditis may be due to the same cause.

Thrombosis is not an uncommon primary necrosis of the endocardium of the heart play but little part; it is proliferation of the intima, the thrombus is frequently found in the vessels in other organs.

LUNGS.

In the course of our investigation we found it necessary clearly to define the terms. The simplest conception of

mose gland; the bronchi represent the excretory ducts, and the lining epithelium of the alveoli the secreting epithelium of the gland. Each lung is divided into lobes by deep constrictions extending nearly to the hilum. The lobes are subdivided into the lobules, and each lobule into a number of small areas which, carrying out the analogy with the gland, we propose to call acini.¹ The acinus is composed of the terminal bronchus and the various air spaces connected with it. The acinus corresponds to the lobule of the lung as described by Miller.

On a section made through the interior of the lung the lobules cannot be distinctly made out. If the pleural surface of the lung of an adult be examined, a network of dark lines usually can be seen, which are due to carbon pigment in the tissue, surrounding the lymphatic plexus of the pleura. These lines more or less clearly mark out the lobules of the lung and they always correspond to the interlobular septa, although they may enclose several lobules. If a section is made perpendicular to the pleura, particularly in an œdematous lung, small bands of connective tissue can be seen extending from the pleura between the lobules. Usually the lobule does not receive a complete investment with connective tissue. From the larger masses of connective tissue small septa are given off which penetrate within the lobule and to a slight extent separate the acini. (Plate XXX., Fig. 1.) The lobules vary in size, and according to Laquesse and D'Hardeviller may each contain from 50 to 100 acini. On the pleura they have a more or less triangular shape; the base corresponds to the pleura, and the bronchus and artery enter at the apex. In the interior of the lung they are naturally of irregular shape. The lobules and their relations are well shown in corrosion specimens of lungs which are incompletely injected from the bronchi, so that only some of the lobules are filled with the injection mass. The bronchus and artery after entering the lobule divide rapidly but not

¹ In describing this ultimate area of the lung as an acinus we have followed Orth. In the admirable article on the pathological anatomy of the lung contained in his textbook he says, "Man nennt einen solchen Abschnitt des Lungenparenchyms, der aus einem Endbronchus hervorgeht einen Acinus."

dichotomously. The artery accompanies the bronchus throughout. The veins always run in the interlobular septa and in the small masses of connective tissue which imperfectly separate the acini.

According to the description of Miller the terminal lobule which we call acinus is formed in the following manner: The bronchus after a final division terminates in the bronchial passage (bronchiole) from which:

which has a greater diameter

XXVIII., Fig. 2; Plate XXVII

sage after a constriction termin:

atria (Plate XXVII., Fig. 4), fro

of large air sacs (infundibula)

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eral lymphatics into the lymphatic plexus of the pleura. This is certainly the case with regard to lymphatics in the lung adjacent to the pleura, but we are not able to say positively that it holds for the lymphatics everywhere. We have never found any communications between the central and the peripheral lymphatics of the lobule. There are no distinct valves in the central periarterial lymphatics; in the peripheral they are very numerous and their position shows that the direction of lymph flow is towards the pleura. The large lymph vessels receive numerous smaller ones. A very effective valve is placed at the entrance of the small vessel into the large, due to the extension of the walls of the small vessel a considerable distance into the larger. The peripheral lymphatics accompany the veins, though they have not the same definite relations with these as have the central lymphatics with the arteries.

There is but a small amount of lymphoid tissue in the lung. In the walls of the bronchi, and to a less extent in the walls of the arteries and veins, there is considerable infiltration with lymphoid cells. In various places definite collections of lymphoid cells forming microscopic lymph nodules are found. These are always in close relation to lymphatic vessels; the mass of cells often projects into the vessel and is separated from its lumen by only a single layer of endothelium. Such small lymph nodules in the interior of the lung are more nearly related to the arteries than to the bronchi and veins. They are also not infrequently seen beneath the pleura. The lymphoid cells may extend from them for a considerable distance in the walls of the partitions. We have never found any such collections of lymphoid cell in the wall of the acini.

The macroscopical appearance of the lungs presented considerable uniformity. As the cases were mostly in children, there were rarely fibrous adhesions between the pleural surfaces. The lungs were usually voluminous, and contracted but little on opening the pleura. In most cases there was considerable injection of the vessels, and in some this was extreme. The most constant lesions were small areas of solidification which varied considerably in size. In many

cases they were sharply limited to lobules, in others they were much smaller, and in some they involved a number of lobules. The character of the solidification varied. In some cases the foci were so sharply circumscribed as to resemble tuberculous areas, but generally they were more diffuse and faded gradually into the surrounding tissue. They were usually of a reddish color, and the tissue around them was deeply injected, but in some cases they were grayish-red or even gray. Even when the solidification affected considerable areas it was not homogeneous; there were centres slightly elevated which were firmer than the other tissue. It was evident that these large areas were formed by the confluence of adjoining small areas. Such areas of bronchopneumonia were found in 131 of the 220 cases examined, or in 60 per cent. Of the 131, the areas were discrete in 76 and confluent in 55. In the majority of cases the posterior portion of the lung was affected and especially the lower lobes. This was particularly true of the co-
rence of the discrete or of the confluent
to bear any relation to the vascu-
lar present, nor does the presence of
appear to influence the extent of the
however, a very definite relation
between the pleural membrane in the lower respiratory
tract and the occurrence of bronchopneumonia. The
presence of inflammation in one or more of the lower
respiratory organs, namely, the glottis, larynx, trachea, or bronchi,
was present in 72, or 72 per cent., of the cases, while in
cases it was present only in 59, or 45 per cent. (of 131 cases
of interest is the fact that of 76 cases in which no
tracheotomy was performed) all but 19 had
bronchopneumonia. The cases of bronchopneumonia may be
further be divided into four groups:
I. Twenty-seven cases in which the inflammation
was involved. Of these, in 13 the inflammation was in the
upper lobe, in 14 the right. The areas were in the upper
in the middle in 4, and in the lower lobe in 19. Of these
were confluent; in 19 discrete.

II. Twenty-one cases in which two or more lobes of one lung were involved. The left lung was affected in 8, the right in 13. All the lobes of the right lung were affected in 8 cases, the upper and lower in 5. In 13 cases the areas were discrete, in 5 confluent, and in 3 both discrete and confluent. These figures show that the right lung is more likely to be affected than the left.

III. Twenty-six cases in which one or more lobes of both lungs were involved. The lower lobes of both lungs were affected in 8 cases; the foci were discrete. All the lobes of the right lung with one lobe of the left lung were affected in 7 cases; the foci were discrete in 2, confluent in 3, and in 2 both discrete and confluent. Of the remaining 9 cases one or two lobes of each lung were involved; the foci were discrete in 9, confluent in 1, and in 4 both discrete and confluent. This shows further that when the affection involves both lungs it is more extensive in the right than in the left.

IV. Fifty-seven cases in which all the lobes of both lungs were affected. The foci were discrete, affecting mainly the posterior portion of both lungs in 30 cases, confluent in 12, and both discrete and confluent in 15.

In two cases, both associated with abscess, organizing pneumonia was found. In no case was there a definite lobar pneumonia, although in some of the most marked confluent cases but little of the lower lobes contained any air. On section the areas were usually smooth, though in some cases, particularly in adults, the cut surface was fully as granular as in lobar pneumonia.

The bronchi were usually affected. The mucous membrane of the large bronchi was reddened and covered with exudation, and usually small drops of pus could be forced from the small bronchi on pressing the cut surface of the lung. In 43 cases there was a fibrinous exudation in the bronchi, forming in the larger bronchi a distinct membrane, and completely filling the smaller. The membrane was similar to that in the trachea.

The tissue in the vicinity of the foci of solidification was generally œdematous, but there was but little general œdema

of the lung comparable to that so commonly found in adults. The œdema was in distinct relation to the inflammation; it was not the general œdema due to disturbances of the circulation.

Where the areas of bronchopneumonia adjoined the pleura the pleural surface was usually slightly cloudy and in some cases there was an evident fibrinous exudation confined to the small areas. In 18 cases there was pleurisy with fibrinous exudation, in 1 sero-fibrinous exudation, in 7 empyæma, in 1 pyopneumothorax, and in 1 hæmorrhage into the pleural cavity. A very common lesion of the pleura consisted of the presence of small ecchymoses, irregular in shape, and from 1 to 10 mm. in diameter. They were irregularly distributed over the surface, but were most numerous over the lower and posterior surfaces of the lung.

The lungs were examined microscopically in 133 cases. Those cases especially were selected for microscopic examination in which the tissue was best preserved and in which the lesions seemed to be most important. There was a close general agreement between the character of the lesions as determined by the naked eye and the results of the microscopic examination. In several cases in which no bronchopneumonia appeared macroscopically the microscope showed very small areas limited to an acinus or part of one.

From the examination of so many cases of bronchopneumonia, representing as they did lesions in various stages, it was possible to form a very definite idea of the nature and extension of the process. What we saw in the earliest lesions were found in those cases in which there was little or no change to the naked eye. As a rule there was considerable uniformity in the extent of the lesions in the sections from the same case.

The process begins in the atria (Plate XX, Fig. 4), with congestion of the vessels, cellular infiltration, and exudation into the lumen. As a rule the process is involved with the atrium (Plate XXVI, Fig. 1, XXVII., Fig. 5), but in several cases the process was limited to the atria. No cases were seen in which ex-

in the terminal bronchi without affection of the atrium. From the atrium the exudation extends to the air sacs and alveoli connected with them. In some cases all the air sacs were affected, in others only a few. The exudation either fills the sacs or clings to the walls, leaving in the centre a round or oval space with sharp cut edges, evidently due to the presence of air. In a number of instances the solidification of the tissue was limited to single acini (Plate XXVIII., Fig. 1), while the adjoining acini were free from exudation. It would be possible to use the term "acinous pneumonia" to distinguish this condition. The larger areas are due to a similar process affecting a number of acini. The infection of these may have been simultaneous or have extended from one to the other. We are inclined to believe that there is little, if any, lateral extension from one acinus to another through the intervening walls. We have repeatedly seen cases in which all the air spaces of an acinus were filled with exudation while the spaces of adjoining acini were free. Moreover, when adjacent acini were affected, the character of the exudation in the different acini often varied. The large foci of solidification do not show the homogeneous character which would come from a lateral extension of the process. The general arrangement is that of a centre with complete solidification, and at the periphery a very irregular outline formed of single affected acini. Occasionally in these acini the process is limited to the atria, but generally it is more advanced. When the process extends it is by way of the bronchus; successive acini are infected when the bronchial infection reaches the terminal bronchi supplying them. From a single acinus in any part of a lobule, all the acini of the lobule can become affected. It seems to us that this better explains the frequently sharply lobular character of broncho-pneumonia than the supposition that it is due to lateral extension. It is very striking to see how sharply the process is often limited to the lobule. (Plate XXX., Fig. 1.) On one side of the thin connective tissue imperfectly separating the lobules we may see complete solidification of a large area and on the other normal or slightly emphysematous tissue.

In cases of marked bronchitis, there was exudation in the lumen of the bronchi; the affection spread through the bronchial wall, but the lung is relatively unimportant because little lung tissue is affected.

The character of the exudate varies in the different cases. It was generally of the same character in different foci of the same case, but it varied in character from foci and even in a single focus. In some cases around the larger bronchi contained many cells (Plate XXVIII., Fig. 4), while in other cases it was cellular. Sometimes a single acinus contained many cells. The most numerous cells were the polymorphous ones. The only ones are the polymorphous leucocytes recognized by the irregular shape of the nucleus, the granules in the protoplasm, and the cell membrane. They are found in the lumen of the air sacs and alveoli, in the process of migration. The nuclei are generally well preserved, but in some cases the nuclei are disintegrated. The function of the nuclei. They frequently contain pneumococcus particularly was seen. Next to the polymorphous leucocytes are those which in their general appearance are so-called transitional leucocytes. They are generally larger than the polymorphous leucocytes, but they vary considerably in size. Their shape is round, oval, or curved; the nucleus is distinct, and fine chromatin granules are present in the nucleus. Nuclei are occasionally irregular in shape as the nuclei of the polymorphous leucocytes. The protoplasm is not at all or contains granules, but not a sharp outline. The number of cells varies greatly in the different cases, sometimes numerous or almost the exclusive cells, while in others but few were found. The cells for other cells to a limited extent.

lymphoid and plasma cells, or nuclear detritus sometimes are found enclosed in them. Bacteria of any sort are rarely seen within them. These cells are similar to some of the emigrated cells found in the rabbit's cornea after inflammation.¹ In the cases where they were numerous in the exudation they were also found in the septa and in the blood vessels, but they were never seen in the act of migration as were the polynuclear leucocytes. Pratt has described similar cells in acute croupous pneumonia, and in some of his cases they were the only cells in the exudation. The great irregularity in their numbers was striking and could not be explained by the duration of the process or the variety of the organisms causing it. Although it is possible to find certain cells which, judging from the character of the nucleus alone, it is difficult to distinguish from the polynuclear leucocytes, they certainly are not converted into these in the exudation. It is much more difficult to distinguish certain of them from the cells which are formed by proliferation of the lining epithelium. The cells in the exudation which we regard as formed from the epithelium vary greatly in size, but are generally larger than the exudation cells. They have a round or oval vesicular nucleus, and clear or finely granular protoplasm, which often shows a peculiar condensation around the edge. They are very similar to the large cells found in tuberculous bronchopneumonia. Their numbers varied greatly; in some cases they formed the majority of the cells enclosed in the exudation. In many cases there was marked proliferation of the lining epithelium with numerous nuclear figures, and the

¹ Councilman has described these cells under the name of nongranular leucocytes. They appear in the inflamed area of the cornea after the polymorphonuclear emigration has subsided. They are the same cells which are found in the sinuses of the lymph nodes and in other situations, and are probably found in greater numbers in the various lesions of typhoid fever (Mallory) than in other processes. It seems to us that they are of endothelial origin, formed from the endothelium of the blood and lymph vessels. They are generally described by the writers on the blood as mononuclear or transitional cells. We do not believe that they ever undergo a further metamorphosis resulting in the formation of the polynuclear leucocyte. Cells of a very similar character may be derived from the epithelium of the peritoneum, pericardium, and pleura, and from the alveoli of the lung. We shall refer to these cells hereafter as mononuclear leucocytes.

cells in the spaces were similar to those still attached to the walls. The proliferation of the epithelium seemed to take place in two ways. In some cases the cells were swollen, increased in number, retained their flat shape, and adhered to one another, forming a ring around the alveolus. This epithelial ring was often separated from the wall. In other cases the epithelium was swollen, and the cells took the shape of low columnar epithelium. In places a large number of these cells were found adhering one to another and to the

separated. The red corpuscles were more frequently associated with the fibrinous exudation, though in some cases not a trace of fibrin was found in the hæmorrhagic foci. In several of the cases there was a peculiar form of exudation which frequently accompanies tuberculosis. In these cases there were large areas in which all the spaces were filled with a mass which under a low power appeared perfectly smooth and hyaline. Under an immersion a fine, even granulation could be distinguished in it. It closely filled some of the cavities and had slightly shrunk from the walls of others, leaving small crescent-shaped clear spaces. In the interior of the mass small clear circles were occasionally seen. It usually contained numbers of red blood corpuscles aggregated into small masses and occasionally leucocytes. Such an exudation differs from the ordinary serous exudation which is found in oedema. This is granular and does not so completely fill the spaces. It is probable that this exudation is serous, but the serum has undergone some change in passing through the vessels or afterwards. It is most often found in combination with hæmorrhagic exudation, rarely with the fibrinous or purulent.

The amount of fibrin in the exudation varied. In some cases it was so abundant and so evenly distributed that the microscopic picture was that of a typical croupous pneumonia. In other cases but a small amount was present. As we have said, it was always more abundant in the vicinity of the larger bronchi (Plate XXVIII., Fig. 4), and was occasionally limited to this situation. When present in very small amount it often formed a distinct rim around the alveolar wall as has been described by Ribbert. We were never able, however, to find any indication of its formation in connection with cast-off and necrotic lining epithelium. The character of the fibrin varied, forming in some cases a very fine reticulum; in others the fibres were coarse and irregular in size. In several cases the fibres were greatly swollen and fused together, forming irregular hyaline masses which no longer gave the typical staining reactions for fibrin. Fibrin often in the

form of single filaments was also found in both in the capillaries and outside of them.

In most cases the bronchi at a distance pneumonia showed evidences of inflammation frequently intact. In other cases bronchi were pronounced as to form the most prominent feature. In the slightest degree of inflammation the bronchus was intact (Plate XXX., Fig. 3) and there was no cellular exudation composed of polynuclear cells in the lumen. The same cells were found in the alveoli and between the epithelial cells. In a few cases there was exudation in the bronchi without any evidence of inflammation of the walls; the exudation evident in the bronchus from some other focus, or it may be derived into it from the handling of the tissue wall. In more severe forms of bronchitis there was exudation in the lumen, the epithelium was partially detached, cells were partially stripped from the wall, the wall was deeply injected, and the tissue was densely infiltrated with cells. (Plate XXI.) In some cases epithelial cells often adhered to one another, forming clotted masses lying in the exudation. The detachment of the epithelium was due to the accumulation of exudate in it. In some cases a small amount of granular material, often showing the same small circular structure within the tubules of the kidney, was found in the alveoli; in others a large mass of hæmorrhagic or purulent exudate. The exudation within the bronchi was composed of polynuclear leucocytes; in some cases it was hæmorrhagic. The same nongranular leucocytes were found in the alveoli were also present, and in some cases large cells regarded as derived from the lining of the alveoli. In all cases where the inflammation was intense cellular infiltration of the walls was present. Numerous of the infiltrating cells were the lymphocytes. These cells were both scattered diffusely and collected in groups. The connective tissue of the wall were swollen and proliferating as shown

of numerous nuclear figures. Nuclear figures were also abundant in the plasma cells. The cellular infiltration almost invariably extended from the bronchus to a considerable distance into the surrounding lung tissue. (Plate XXX., Figs. 2 and 3.) The walls of the adjoining air spaces were thickened, infiltrated with the same cells, and the epithelium swollen and proliferating. In some cases this was accompanied with exudation. This extension of an inflammatory process from the wall of a bronchus into the adjoining lung tissue is very different from the ordinary bronchopneumonia. In this latter process the infecting material, whatever its character, is carried into the terminal bronchi and atria, and lateral extension plays little or no part in the process. The lateral extension is seen only along the larger bronchi in which there is intense inflammation, and the character of the exudation may be totally different from that in the lung elsewhere. The bronchi seem often to form the centre of a large area of pneumonia, but further sections will show the relation of this pneumonia with terminal bronchi which have come from some other point of the large trunk which is affected or from neighboring bronchi. We have repeatedly found cases in which there was extensive bronchopneumonia without any evidence of bronchitis in the larger vessels; the foci were distinctly terminal. We are aware that the prevalent idea is that the exudation is due chiefly to a lateral extension from the bronchus, but we think this idea has been due to the fact that the cases examined have not been sufficiently numerous or early enough, and the method of examination by serial sections has not been generally employed.

The cases of bronchitis with distinct membrane formation due to an extension of the diphtheritic process from the trachea into the bronchi deserve especial mention. In 43 of the cases membrane was found in the bronchi, generally in those of larger calibre. In a few cases it was found in all the smaller bronchi as well. No trace of epithelium was found in the affected bronchi. The membrane was fibrinous in character and seated on the membrana propria. There was no hyaline or fibrinoid degeneration of the tissue similar to

rise to the formation of small blebs, but no general interstitial emphysema was found.

In the œdematous lung between the numerous foci of pneumonia, particularly in the posterior borders, there were granular material, evidently coagulated albumen, and a few cells. As we have said, the general œdema so common in adults and probably due to disturbances in the circulation was never found. The œdema we found was inflammatory in character.

In 14 of the cases there was necrosis, often combined with definite abscess formation. Abscesses were noted at autopsy in 11 cases. The abscesses were more common in the cases of longer duration, although they were found in 2 cases in which death occurred on the third day, and in 1 on the fourth. The cases of long duration were in the fifty-third and forty-ninth days of the disease. The average duration of the 14 cases in which they occurred was 17 days. The necrosis and abscess formation was due to infection through the bronchi. The foci seemed in some cases to begin as terminal foci similar to the foci of pneumonia in other cases, though extension through the walls of the bronchi could not be excluded. In some cases there were sharply circumscribed areas of necrosis, involving but a few of the air spaces of an acinus. In the same cases there was found necrosis of the bronchial wall and of the adjacent air spaces. There was little or no inflammatory reaction around the necrotic tissue, and both the air spaces and walls were so filled with masses of diphtheria bacilli as to appear under a very low power as brightly stained areas. In other cases the tissue was partially broken down and necrotic, and filled with degenerated pus cells and red blood corpuscles. In one of these cases, in the midst of the necrotic material, there were small islands of tissue, generally around the larger vessels, which were well preserved and infiltrated with pus cells. In other cases the abscesses were of a more chronic character. Nothing of the lung structure could be recognized in the interior and there was extensive purulent or fibrinous exudation in the surrounding tissue with infiltration of the interstitial

tissue with leucocytes and lymph infiltration often extended a lo around the abscess. About som an extraordinary absence of infl edge of the abscess the necroti but little exudation and cellular one case small areas of necrosi beneath the pleura.

The interstitial tissue of the l that it deserves especial mention to the cellular infiltration of the nection with the exudation into t extension of the peri-bronchial cases of abscess there was not o the connective tissue in the vic affected distant parts of the lun abscess formation. In some cas seemed that the abscess had already the seat of an interstit addition acute interstitial process to be of the same nature as th We never found this process alo by bronchopneumonia or bronc interstitial tissue was thickene The most intense infiltration was and in the small fibrous septa. tive tissue of the pleura and tl might or might not be accomp spaces. From all these places i the air spaces, becoming less i infiltrating cells were almost excl cells; only occasionally were p among them. The large plasm methylene blue and gave a striki The same cells as those in the large numbers in the small vein dition was found more frequer were present in large numbers a

ing agents, but it was also found in equal intensity in cases in which the infection was due to streptococci and pneumococci. In none of the cases were bacteria found in immediate connection with the interstitial processes. Nuclear figures were found both in the cells within the vessels and in those in the tissue. There was often marked œdema of the connective tissue septa, and in some cases a great deal of fibrin was found in it, even in cases where the adjoining air spaces showed no fibrin. The œdematous tissue contained numbers of lymphoid and plasma cells, and large cells similar to the cells of supposed epithelial origin in the alveoli, lying loosely in the tissue. The stellate cells of the connective tissue were swollen and occasionally contained nuclear figures.

In a very large number of cases, both in those in which death occurred very early and in those in which it occurred late in the disease, peculiar bodies were found in the capillaries, giving the impression of masses forced from a larger into a smaller tube. (Plate XXIX., Fig. 5.) The bodies were often bifurcated at one end, and the bifurcation extended into the junction of two capillaries as a riding embolus. It was at first supposed that these bodies were composed of hyaline fibrin and represented the hyaline thrombi so often described in the capillaries of the lung. They stained brilliantly with the nuclear stains, but did not give the reaction for fibrin. In some cases a small amount of granular protoplasm was found in connection with them, and their evident nuclear character was shown by strands and granules of chromatin. Every transition was seen from such structures of evident cellular character to homogeneous masses which took the nuclear stain. They were not confined to the areas of bronchopneumonia, but were uniformly scattered through the tissue. The only cells of a similar character are certain of the cells of the bone marrow, and we have considered these cells in the capillaries to be marrow cells which were brought to the lung as emboli and forced into vessels of a smaller lumen than their diameter. No such cells were found in the sections of the larger vessels of the lung, though they were

found in the vessels of the marrow. No 1 found in the capillaries, and it seems possible hyaline thrombi which have been described in these large marrow cells. Pratt has described the capillaries in cases of acute lobar pneumonia where they were numerous and they were not occluded. Possibly the cells only occasionally find their way into the blood, and they may remain in the capillaries and undergo necrosis, so that they have the characteristic appearance and stains of dead cells. In several cases numbers of the large eosinophilic cells from the marrow were found in the vessels.

Thrombi were occasionally found in the arteries and veins. They were in some cases completely occluding. In quite a number of sections of leucocytes with fibrin between them were found lying loosely in the lumen. In some cases phlebitis was found. In both instances large areas of bronchopneumonia. In some sections collections of polynuclear leucocytes benched the lining and infiltrating the wall. In the other section was similar to that described in a case of meningitis. The endothelium of the vessels was often forming festoons, and beneath this were cells of an epithelioid character. Many of these closely the large cells described in the eosinophilic occasional polynuclear leucocyte was found.

Chronic interstitial processes, evidencing healing and consisting of thickening of the alveoli, and of organization of the exudate were found in several of the more chronic cases. Particularly marked in one. This was a child that died on the one hundred and eighth day of life. The child had entered the hospital with scarlet fever. They were followed by whooping cough, inflammation of both middle ears and mastoids, necrosis of the lungs. Two months before death there was a severe pneumonia, followed by resolution and

weeks before death. At the autopsy there were areas of solidification of the right lung; the solidified areas were very firm and dry. On microscopic examination there was great thickening of the walls of the air spaces, due partly to a general increase in the tissue of the wall, and partly to a formation of connective tissue just beneath the epithelium. The epithelium was in part converted into low cylindrical epithelium similar to that in the terminal bronchi, in part it was simply swollen. The exudation was fibrinous, with the fibrillæ swollen and indistinct. The masses of fibrin were in many cases completely or partially covered by a layer of epithelial cells. The formation of connective tissue inside the cavities took place in two ways: in one by a growth of a polypoid mass of connective tissue from the wall retaining the covering epithelium over it, in the other by the penetration of the fibrinous exudation by connective tissue forming cells, leading to a definite organization of the exudation. In one section a long process of organizing tissue was followed from an atrium where it was attached, through the whole extent of the acinus. Polypoid masses of connective tissue, which possibly represented the last stages of organization, were frequently found in the small bronchi, and the formation seemed often to proceed from these and the atria, extending into the air spaces. One well-marked case was found in a man thirty years old, who died on the second day after entering the hospital. It was evident in this case that the lung affection was an old one, while the diphtheria was a secondary infection. In this case the growth of polypoid masses of the connective tissue into the small bronchi and atria was well marked.

The lymphatics were affected in a large number of cases, and were easily demonstrable. In all cases of œdema of the interlobular tissue the lymphatics in it were enormously dilated and contained some granular material. They were more generally dilated here than around the arteries. In many cases they contained large numbers of cells and in some they were filled with fibrin. The cells within these dilated lymphatics attracted particular attention from their character. There were few red corpuscles among them and

comparatively few polynuclear leucocytes were abundant in the exudation around the principal cells were lymphoid and plasma, eminently phagocytic and in all respects like cells in the exudation with the air sacs. They were in size, had abundant homogeneous protoplasm and oval vesicular nucleus. The origin of these cells seemed improbable that they had entered from the air spaces; on the other hand in some cases no proliferation was seen in the interstitial tissue. In one case in which there was great proliferation of the interstitial tissue and the lining of the dilated lymphatics were found in the interstitial space of the pleura containing numbers of these cells (Fig. 4.) The endothelial cells were so small and numerous in number that the section of the vessel wall was completely surrounded by proliferating endothelial cells. Certainly the large cells in the lumen of the dilated lymphatics, and it seems probable in some cases the cells may have originated in the interstitial tissue to some other point in the vessel where proliferation was not taking place. These large cells were numerous in the periarterial lymphatics.

The lymphoid tissue of the lung seemed increased. Most of the autopsies were made within a few days of death and in these there is more of such tissue than in the normal lung. In one section a small lymph node was found in the lung containing a necrotic centre and surrounded by the lymph nodes.

In 18 cases there was a fibrinous exudation over the entire pleural surfaces. In addition there were frequently small areas over the bronchi where the pleura was either slightly cloudy or covered by a thin exudation. So many sections were examined that it was generally so well preserved that the relation of the exudation with the epithelial lining of the bronchi and the tissue could be easily seen. It was interesting to see in various these relations could be. The exudation

fibrinous with a varying admixture of red blood corpuscles and polynuclear leucocytes in the different cases. In some cases the exudation was on the surface and the epithelium could be distinctly made out beneath it; in other cases the epithelium had disappeared. In several cases the exudation was beneath the epithelium either in the meshes of the connective tissue or immediately beneath the epithelium, which it had elevated. The character of the epithelium was always changed. The cells were large, the protoplasm abundant, granular, and somewhat colored with the staining reagent, the nuclei large and rich in chromatin. Nuclear figures were numerous. The connective tissue was simply infiltrated with fibrin. The hyaline fibrinoid metamorphosis of the connective tissue so often seen in connection with the diphtheritic membrane was never found. In several cases very peculiar relations of the fibrin and epithelium were seen. In one case in particular the surface of the fibrin was almost totally covered with proliferating epithelium, and in the fibrin itself numerous spaces were found lined by similar cells. This condition was evidently due to a growth of the epithelium into the spaces of the fibrin, or to folding in of the irregular surface. A similar condition was found in the fibrinous exudation in one of the cases of pericarditis. In another case there was a thin layer of fibrin over the epithelium and above this a similar complete row of epithelium, then fibrin, and occasionally a shred of connective tissue. It seemed in this case that a part of the parietal pleura had been stripped off, and in this the exudation was beneath the epithelium, while on the surface of the lung it was over it.

Older cases were found representing all stages of organization. In one case the pleura was thickened, and elevated in folds which were covered by swollen epithelium similar to columnar epithelium, and without a trace of exudation. In all cases in which the pleura was affected there was marked proliferation of the epithelial cells of the adjoining air spaces.

In the microscopic examination of the lung sections the presence of bacilli and their relation to the lesions was noted. The examination was made on sections stained in the routine

manner with methylene blue and bacteria stain extremely well by this. In the sections studied were old and faded, bacteria were not visible, or on a small number of cases. More attention was given to the lesions than to their microorganisms. It has been made in 97 of the 133 cases. In comparing the results of cultures with those of the sections there was considerable discrepancy. In the case of the pneumococci, microscopic examination in sections and cultures were considered the prime infection. In cases where they were not found in the cultures, it was due to the difficulty of the organisms to culture. In the case of other organisms it may be compared with the growth prevented by such rapid growth of streptococci or diphtheria bacilli in such small numbers as not to be detected by examination of the tissue. We realize that it is extremely difficult, if not impossible, to get accurate results where cultures are not made a matter of routine. The results of the sections were whole valuable and fairly accurate. In the case of certain organisms, and possibly the pneumococcus, were overlooked. The pneumococcus was found 11 times in the sections and 11 times in the cultures. Other organisms, such as the streptococcus, were found more often in the sections; diphtheria was found 38 times in sections 38 times; the streptococcus was found 29 times in sections 29 times. In the great variety of micro-organisms was found in such numbers and in such relations that they were considered as the infectious agents. They were occasionally found in the blood and without any apparent relation to the disease. They were to be saprophytes and were not pathogenic.

The diphtheria bacillus was found in the sections and in the cultures.

4; Plate XXIX., Fig. 5) alone in 18 cases, in connection with the streptococcus in 6 cases, with the pneumococcus in 9, and with the streptococcus and the pneumococcus in 5 cases. The micro-organisms were usually present in very large numbers. The records frequently mention "large masses" or "enormous numbers." When only a few were found they were usually confined to the bronchi, while in the lung elsewhere streptococci or pneumococci were found. The diphtheria bacilli were found in connection with all the inflammatory lesions of the lung. They were frequently the only bacteria found in definite foci of bronchopneumonia. In these cases they were in the air spaces and generally in enormous numbers. (Plate XXIX., Fig. 5.)

The character of the exudation caused by them varied. Usually little or no fibrin was found, and it was frequently purulent and hæmorrhagic. The bacilli were both free and enclosed in pus cells. The cells enclosing them seemed to be exclusively polynuclear leucocytes. In some cases, owing to the number of bacilli in the cell, the nucleus could not be distinguished with sufficient accuracy to determine the character of the cell, but they were never found with certainty in the mononuclear leucocytes or in the larger cells of epithelial origin. The diphtheria bacilli were the only micro-organisms in four cases of abscess of the lung. They were found in enormous numbers in the necrotic tissue of the abscess and in the wall. In two of the abscesses there was but little reaction in the surrounding tissue. They were also found in equally great numbers in areas of necrotic tissue which had not yet broken down to form abscesses. In one of these cases there were large masses of bacilli marking out the air spaces, of which all the cells in the walls were necrotic. (Plate XXIX., Fig. 5.) In one case they were found in large masses in air spaces filled with serous exudation and had produced neither suppuration nor necrosis. It could not be assumed that such an enormous growth of the bacilli could be post mortem, for as a rule the autopsies were made but a short time after death, and a similar growth was not found in other situations as in the pharynx. They were found in the membrane of the

bronchi, chiefly in small masses on or near the membrane. In many cases the membrane contained few cocci, but when they were in large numbers in the air spaces they were generally well preserved and stained. In some cases branched forms and long degenerated cocci were seen. There was no marked difference in the lesions when the streptococcus or the pneumococcus accompanied the diphtheria bacilli.

In four of the cases of abscess formation found in such numbers and relations that they were regarded as the causative agents. In one case the abscess was thought to be produced by the streptococci, while in the others the streptococci were found elsewhere in large masses. The character of lesions was found in the streptococcal abscesses varied from abscess formation to fibrinous, purulent, or hæmorrhagic exudation. The exudation produced by the streptococcus was more fibrinous than that produced by any other organism excepting the pneumococcus. In one of the cases of pleurisy with fibrinous exudation they were found in large numbers in the pleural exudation and in the interlobular lymphatics.

Pneumococci were associated with abscess formation in three cases and were regarded as the cause of this in one case. They were by far the most frequent cause of abscess formation. They were found either free in the exudation or associated with polynuclear leucocytes. They were frequently found in the older parts of a focus and present in greater numbers in the lesions appeared to be more recent, and the exudation was principally serous. This we have seen in the case in acute lobar pneumonia. We have found the pneumococcus associated with every form of exudation we have described, but somewhat less frequently than the streptococcus.

Staphylococci were extremely rare in the cultures. We have so commonly found in the cultures. We have not associated them with any of the lesions, and

play little or no part in the production of the lung lesions of diphtheria.

The histological examination points clearly to the fact that infection takes place through the bronchi. Flexner and Anderson found that when small quantities of diphtheria bacilli were injected into the trachea, typical foci of bronchopneumonia developed. In this experimental form also they found the first lesions in the atrium. Boassohn thinks that the infection generally takes place by the bronchi, but may also take place by means of the blood and lymph. He supposes that when the mouth becomes dry the micro-organisms may be lifted from the dry surface and carried with the air into the lung. Katzenstein thinks that the infection usually takes place by the bronchi, but that infection by the blood is most probable in the small foci in the lower lobes. Mya in an elaborate article on the subject concludes that there are two factors, one mechanical and the other biochemical. One of the most fundamental causes, according to him, lies in the affection of the lymphatics and the disturbance of the lymph circulation. There may also be disturbances of the blood circulation, all of which produce conditions favorable to the action of micro-organisms. We have not been able to find these favorable conditions, and have called attention to the absence of circulatory œdema. We do not believe that the infection is embolic to any extent at least. The lesions are different from the embolic pneumonias. We have only found in one case evidences of the embolic action of the diphtheria bacilli; the few which enter the circulation and are found in cultures from internal organs are certainly not the cause of the lesions found in these organs.

Summary.

There is no organ in the body in which lesions accompanying diphtheritic infection are so generally found or so serious as in the lung. In very many cases they are so extensive that death may be considered as due rather to the condition of the lungs than to the throat affection. We have frequently found extensive lesions on microscopic examination even

when the lungs presented little or no change to the naked eye. It seems probable that the frequency of these lesions may be due to the fact that most or all of our cases were treated with antitoxin, and that those in which the lung complications were not present, or at least not severe, recovered. This should always be taken into consideration in the results of antitoxin treatment. Antitoxin cannot influence the pneumococcus or streptococcus infection.

The most common lesion is bronchopneumonia. The term implies both the manner in which infection takes place and the relation of the foci to the bronchi. The process begins as an infection of the atria and from here extends. It may be limited to single acini, to lobules, or to groups of lobules. There is but little lateral extension of the infection through the walls of the alveoli or the bronchi into the surrounding air spaces. Acute inflammation of the larger bronchi usually accompanies the bronchopneumonia, but is not constant. Atelectasis varying in extent from one to several lobules, or even confined to a few air spaces, is very commonly present. The same is true of emphysema. True acute lobar pneumonia was never found. The cases resembling this were found on closer examination to be cases of extensive confluent bronchopneumonia. General œdema of the lung comparable to the circulatory œdema of adults was never found, although inflammatory œdema was common. The character of the exudation varies greatly. It may be fibrinous, hæmorrhagic, serous, or almost entirely cellular. In a few cases a hyaline exudation similar to that found in tuberculosis was present. The cells in the exudation are partly leucocytes, partly cells derived from proliferation of the lining epithelium. Lymphoid and plasma cells also are found in the exudation. Cellular infiltration of the interstitial tissue and productive changes in it are common, both in connection with the acute exudative lesions and apart from them. In some cases organization of the exudation and connective tissue formation within the air spaces was found. Proliferation of the lining epithelium of the air spaces is frequent, and is always more pronounced in the vicinity of the pleura and the connective

tissue septa. It is possible that this is to be explained by the concentration in the lymphatics of substances causing proliferation. Necrosis in some cases leading to abscess is not an uncommon feature.

Large objects considered to be marrow cells which in many cases had undergone degeneration are frequently found in the capillaries, and it is possible that these have been frequently mistaken for hyaline thrombi. Single strands of fibrin are sometimes found in the capillaries and interstitial tissue, but never definite capillary thrombi. Thrombi are occasionally found in the larger vessels. Dilatation of the lymphatics is very common. They may contain coagulated albumen, fibrin, or cells. They are often found packed with lymphoid and plasma cells, and large cells similar to the large cells in the air spaces.

Nothing has shown so well how little the character of a pathological process is influenced by the character of the micro-organism as has the examination of these lungs. Pneumococci, streptococci, and diphtheria bacilli have been found in connection with serous, purulent, fibrinous, and hæmorrhagic exudations, necrosis, and abscess formation. Contrary to the results obtained from cultures, the pneumococcus must be considered the principal agent in producing the lung infection. The diphtheria bacilli are frequently found and may be the cause of bronchitis with membrane formation, of purulent exudation, of bronchopneumonia, necrosis, and abscess. They are often found in the lung in much greater numbers than in any other situation, and there may be but little change in the tissue around them.

We have not attempted to review the literature of the lung lesions in diphtheria. It relates chiefly to the frequency of lung affections in diphtheria and their bacteriology. The literature of the bacteriology of the lung has already been considered.

SPLEEN.

Bizzozero found acute enlargement of the spleen in several of the 24 cases he investigated. In the splenic pulp he found congestion with some hæmorrhage, but the main

changes were in the Malpighian bodies, small foci of necrosis. The lymph node large phagocytic cells which enclosed debris and frequently red blood corpuscles. The spleen enlarged, the pulp increased, the capsule frequently hæmorrhagic. There was emigration due to emigration of leucocytes into the pulp and to proliferation of the pulp. The lymph nodules often filled with cells of foamy character, which enclosed degenerated cells. Oertel confirmed the description of Oertel. In addition a fatty degeneration of the cells was observed. These cells were contained both in the cells of the lymph and in the sinuses. In the centre of the lymph node often large cells of an epithelioid character. There were regressive changes in the cells of the lymph node leading to the formation of nuclear detritus which was removed by the large cells. He speaks of these as necrotic foci. Such foci were never seen in the lymph node. It was necrosis of single cells. Katzenstein described the Malpighian bodies and fibrin around them. He describes necrosis of the lymphoid cells of the lymph node while the reticulum takes the form of a network of cells. Ribbert says the large cells are of endothelial origin. In a recent article Waschlitzky he examined the spleen in a large number of cases to ascertain the frequency of the large cells in the lymph nodes. He regards them as formed from cells which have wandered into the tissue, and claims that they are transition forms. Babes in experimental leucæmia of the lymphoid tissue, congestion of the lymph node, with degeneration of the leucocytes. Flexner found lesions in the lymph node similar to those in the lymph nodes, but the nuclei were not so frequently enclosed in phagocytic cells as in the lymph nodes. In the pulp there was degeneration of the reticular and vascular endothelium and emigration of the cells both within and without the lymph node.

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their walls. Single capillaries with thick hyaline walls and still containing red blood corpuscles were found both in the interior and on the edge of the areas. The hyalin stained more brightly with eosin and dark with iron hæmatoxylin, but not so dark as fibrin. These areas varied greatly in size; in some cases they could be seen in the section with the naked eye, in others they formed but a very small point in the lymph nodule. They were distinctly round or oval when cut in all directions and did not extend along the course of the lymph nodules. The same thing was true of them in the lymph nodes.

In the majority of cases there was considerable nuclear detritus in these areas. The nuclear detritus was chiefly found in the periphery of the area and was contained in the epithelioid cells. All or nearly all of the nuclear detritus came from lymphoid cells, and every degree of degeneration leading to complete destruction could be found in lymphoid cells enclosed in the epithelioid cells. In a few cases the degeneration was so marked that the structure of the area could not be made out; all the cells within it had apparently contributed to the formation of the detritus. Polynuclear leucocytes took no part in the process, did not contribute to the formation of detritus, and were not found even when the necrosis was far advanced. There was a very close similarity between the appearance of these areas in the spleen and young miliary tubercles, just as was the case in the nodules in the lymph nodes. The mode of formation is the same and the epithelioid cells play the same important part. The giant cell formation and the caseation of the tubercle is absent.

In addition to the degeneration of the lymphoid cells in the lymph nodules in connection with the formation of these distinct foci there was a more diffuse form of degeneration which affected the lymphoid cells in the pulp as well as in the lymph nodules. Sometimes almost all the cells in a lymph nodule would be affected. In this form of degeneration the chromatin of the nucleus did not break up into fragments, but became arranged in irregular clumps which often

closely resembled on a small scale clear leucocytes.

Fibrin was found in the lymph was chiefly in the periphery and among the hyaline cells. There was fibrin elsewhere in the tissue. Sometimes it was found to some extent in the lymph, and it was found to some extent in the blood. There was no relation between its presence and the disease. None was found in the nodules composed of nuclear detritus; and it was most abundant where it formed a network of intact nuclei. In this case the fibrin had the morphological and staining characteristics of broad smooth filaments with occasional interruptions along them; some of the filaments suggested hyaline capillaries. Globules of the same hyaline appearance were found in the veins. It stained feebly with eosin, but with iron hæmatoxylin it stained intensely, much more than the cells, and with iron hæmatoxylin it stained more than ordinary fibrin. Fibrin of a great abundance was once found in the lymph in scarlet fever. In one case there was a great deal of the fibrin around the lymph nodules.

In 17 of the 181 cases there was evidence of the arteries in the lymph nodules in the lymph nodules in which focal degeneration was present, and in those without them, so that there was a connection between the formation and degeneration of the arteries. The degeneration of the arteries in the lymph nodules. In those which sometimes accompany the disease were free from it. In the least advanced cases masses of hyalin were found beneath the vessel. In some cases the entire wall of the vessel was replaced by the degenerated tissue. Degenerated nuclei were found in the hyaline tissue, to be formed by degeneration of the

represented an infiltration of the tissue. In nearly all cases the lumen of the affected vessel was narrowed and in some it was almost obliterated. The hyalin stained brightly with eosin and slightly with hæmatoxylin. This condition was found at every age and was generally most pronounced in the more acute cases. The earliest case in which it was found was one which the history gave as of only 2 days' duration, and the most prolonged case was one of 32 days. It was found in the case sixty-four years of age, and the character of the change did not differ from that in the youngest case.

Changes in the veins similar in their general character to those described by Pearce in scarlet fever were found in twelve cases. This change consists in an accumulation of lymphoid and plasma cells, chiefly the latter, in the intima beneath the endothelium. In some cases the cell accumulation was more marked, in certain places producing nodular projections into the lumen; in others the cells were more homogeneously distributed. It varied in degree from a few cells beneath the endothelium to large masses almost occluding the lumen. The cells seemed to extend beneath the endothelium of the veins from the pulp, and the accumulations were most marked where the small veins of the pulp emptied into the veins of the trabeculæ.

Changes in the pulp of the spleen were not so obvious as those in the lymph nodules. There was considerable variation in the degree of hyperæmia, and in several cases there were hæmorrhages. In one case of 32 days' duration there was a good deal of pigment in the tissue, evidently the remains of old hæmorrhages. The most marked change in the pulp consisted in variation in the number and character of the cells enclosed in it. In the normal spleen there are considerable numbers of lymphoid cells outside of the lymph nodules, and in some of the diphtheria cases the number of these was greatly increased. The large lymphoid cells with numerous nuclear figures similar to those described in the lymph nodes were also found. The chief difference as compared with the normal spleen was the large number of plasma

cells in the diphtheria cases. The normal very few of these. They were present in 24 enormous numbers of them were found distributed both generally throughout masses. The masses were so large and incumscribed that with a low power it was difficult to distinguish them from the lymph nodules. They were generally grouped around the small vessels. Where the cells were fewer in number and more distributed they appeared to be enclosed in the pulp, and in some cases numbers were found in the sinuses. These plasma cells were of moderate size, and numerous nuclear figures were present. All of the cases in which plasma cells in large numbers were found died at a late period of the disease; the duration was earlier than 6 days, and the average duration.

It was difficult to determine the extent to which the cells lining the blood sinuses. In certain conditions the character of these cells was depending chiefly upon the varying degree of contraction of the sinuses. In a well-preserved specimen of spleen the cells lining the sinuses, though they did not differ in character from the endothelial cells of the vessels. In a contracted spleen the cells were crowded together, their nuclei had their long axes parallel to the axis of the lumen, and the sinus closed at the end of a gland. In some of the diphtheria cases seemed undoubtedly to be proliferation of the cells. In one case not only were the sinuses lined with masses of them projected into the lumen, but many undoubtedly coming from this source were found in the lumen. Against the view of hyperplasia was the complete absence of nuclear figures. Where numerous the nuclei were pale and distorted. In some the nuclei of cells which were dividing directly into the lumen were too normal in appearance to have originated in such a way. In a few cases

were found in the cells lying free within the sinuses. There was usually no change in the reticulum of the pulp. There was no evidence of hyperplasia in the endothelium of either the arteries or the veins. No bacteria were found in the sections.

Summary.

Lesions of the spleen play but a slight part in the pathological anatomy of diphtheria. The spleen macroscopically does not differ from the normal, except that the lymph nodules usually are more prominent. The most obvious lesion microscopically consists of the formation of foci of epithelioid cells in the lymph nodules, which are of the same character and formed in the same way as those in the lymph nodes. The epithelioid cells are phagocytic, and the nuclear detritus found in these foci comes chiefly from the lymphoid cells which are enclosed in the phagocytic cells. The hyaline degeneration of the vessels is interesting in showing at what an early age this condition can occur. The arteries of the spleen seem to be more liable to this degeneration than the arteries of any other organs in the body. The routine examination of spleens from all sorts of cases shows its great frequency. The presence of large numbers of plasma cells in the organ in the later stages of the disease shows that the spleen may play an important part in their formation. Bacteria were absent and the changes found are not due to their presence in the organ.

ALIMENTARY CANAL.

Smirnow in 1888 reported 6 cases of diphtheria of the stomach with membrane formation, and investigated the mode of formation of the membrane. There is no doubt from the associated lesions of the pharynx that the cases were all true diphtheria. In 3 of the cases the membrane was formed by an inflammatory fibrinous exudation. In the other 3 he described hyaline degeneration of the glandular and surface epithelium, and regarded the membrane as formed of the hyaline material derived from cells. Cronmeyer in his analysis of 459 cases of diphtheria gives 29 cases of diphtheria of

the stomach, but he says nothing of the character of the lesions. He also gives a great number of pathological conditions of the stomach which were associated with the disease, but which were not immediately dependent upon it.

In 5 of our cases a definite diphtheritic membrane was found in the stomach. The extent and distribution of this membrane varied in different cases. In one case almost the entire surface of the mucous membrane beginning at the cardiac orifice was covered with a thick ragged grayish-brown membrane, which was thicker over the rugæ and easily removed, leaving a red granular surface beneath. In the other cases the formation of the membrane was not so extensive and was limited to lines on the surface of the rugæ. The mucous membrane elsewhere was very hyperæmic, and there were small scattered hæmorrhagic points. Microscopical examination showed the membrane to be fibrinous; in no place was there any of the dense hyaline membrane which was so often found in the pharynx. The membrane was always attached to a surface deprived of epithelium, and the fibrin rarely extended to any depth into the tissue below. In several cases it extended from its place of origin a considerable distance over the surface on all sides. The section in one case showed a small mass of membrane, which had a small base of attachment and which projected like a mushroom over the surrounding surface. (Plate XVIII., Fig. 2.) The under surface of the membrane for a short distance was covered by epithelium. It appeared from this that the exudation had first lifted the epithelium over it, and then becoming more extensive had broken through at one place and spread over the surface as a viscid mass turning back the epithelium. In the membrane the filaments of the fibrin seemed to radiate from the stalk of attachment.

Sections of the more extensive membrane showed this to consist of fibrin which had extended over the surface. In one case beneath the membrane there was a loss of substance involving perhaps one-half the length of the glands, with considerable hæmorrhage both beneath and in the mem-

brane. Another section from the same stomach showed several shallow erosions extending nearly to the muscularis mucosa, but without any membrane formation over them.

In addition to the fibrin the membrane contained a small amount of nuclear detritus and red blood corpuscles. The mucous membrane of the stomach both below the membrane and at a distance from it showed numerous alterations. The most striking lesion was the abundant hæmorrhagic exudation. Even in places where there was no membrane and the covering epithelium was intact there was generally extensive hæmorrhage beneath the surface. (Plate XIX., Fig. 2.) Numerous red blood corpuscles were found also deeper down between the glands, and the vessels were generally dilated. The glands in some places were separated by considerable intervals, and in the interstitial tissue were numerous lymphoid and plasma cells and red blood corpuscles. In other places in the mucous membrane there were foci of infiltration with polynuclear leucocytes. Next to the hæmorrhage the most striking alteration was in the glands. In these every degree of degeneration was found. All of the specimens of the stomach examined were from autopsies made only a few hours after death and the tissues were in perfect condition. So remarkable was the preservation of the histological details of the tissue that it seemed unlikely that the stomach contained any fluid capable of causing maceration after death. The epithelium was so perfectly preserved on the surface and in the glands that all changes found were assumed to be pathological. The surface epithelium was everywhere free from degenerative lesion, and there was but slight degeneration of the cylindrical epithelium lining the ducts of the glands. In one specimen there was evident desquamation of the epithelial cells of the peptic glands. The peptic cells lay in the lumen of the gland not only low down, but in the upper part. Their nuclei were in part well preserved, in part they were degenerated. The change was not general and was more evident in some parts of the section than in others. Some of the glands were filled with a mass of cast-off and degenerated cells, both peptic and simple cells.

In some cases the tissue beneath the membrane was necrotic and hæmorrhagic, and the glands as such could not be recognized. Apart from the changes in the glands in the immediate vicinity of the diphtheritic membrane, striking changes in the glands were found in the deeper portions of the mucous membrane. These changes were not more marked in sections containing membrane than in those in which no membrane was present. The slightest changes consisted of swelling of the cells, with an increase of granulation and hyaline degeneration. The nucleus was in part preserved, and in part broken up into detritus. Cells which had wholly undergone hyaline degeneration often lay in the lumen, and where the most extensive degeneration and necrosis were found, numbers of pus cells were contained in the lumen generally showing the same nuclear degeneration. The degenerated cell never showed any tendency to direct nuclear proliferation which was such a prominent feature in the epithelium of the œsophagus, and the covering epithelium elsewhere. None of these changes were focal; a gland showing marked degeneration was often found in the midst of glands completely normal. Sometimes there were areas in which the degenerated glands seemed somewhat more abundant, but nothing approaching a focal lesion was found. It is greatly to be regretted that no sections were examined from a stomach in which no lesions were found. Various bacteria were found in the membrane, but there were very few diphtheria bacilli. In only two sections were the characteristic small groups of these found on the surface. The cultures from the stomach in these cases gave abundant diphtheria bacilli.

The intestinal canal in general showed but few changes macroscopically. It varied considerably in thickness, due chiefly to different degrees of dilatation, but in some cases it seemed undoubtedly to be atrophic. The most marked change consisted in swelling of the lymphoid tissue. The Peyer's patches in some cases were so swollen that they resembled those in an early stage of typhoid fever. The swelling was rarely homogeneous, but the single lymph

nodules, or groups of them, could be distinguished forming round or elongated elevations with pits or furrows between them. The solitary lymph nodules in both small and large intestine were prominent. Considerable care must always be exercised in estimating changes in the lymphoid apparatus in the intestine of the child, for the lymphoid tissue is relatively so much more developed in the child than in the adult. There seems to be some hyperplasia of this in all of the infectious diseases of children, but it is more marked in diphtheria. The duodenum in one case showed a membrane on the surface similar in its macroscopic aspects to the membrane which was found in the stomach of the same case. Microscopically there was superficial necrosis, and on this, and not extending over the adjacent surface, a mass composed of pus cells, nuclear detritus, necrotic epithelium, and mucus. There was no fibrin. In the tissue beneath the membrane there was slight hæmorrhage. In another place there was an erosion which extended nearly to the muscularis mucosa, and which was evidently due to the separation of such a mass. It is remarkable that although fibrin was so abundant in the membrane in the stomach, none was formed in the duodenum.

Exclusive of the stomach the alimentary canal was examined in 60 cases. Usually the examination was confined to the lymphoid tissue and the mucous membrane in the immediate vicinity of it, but in several cases sections were made from a number of places in both small and large intestine. The changes found in the intestinal lymph nodules were of the same character as those found in the lymph nodes, but in general they were not so marked. In the cases of most evident hyperplasia the lymphoid cells extended to the surface, and formed a diffuse infiltration in the tissue below and adjoining. In many cases the so-called germinal centres of the lymph nodules were prominent; in others they were not found. Focal lesions, such as those described in the lymph nodes and spleen, were found in 20 of the cases. The same description which has been given of them in these organs applies to the intestine. The swelling and proliferation of the vascular endothelium was very evident; the nuclei pro-

jected into the lumina of the vessels, causing them to simulate glands. The endothelial cells frequently contained lymphoid cells. In the mucous membrane elsewhere no lesions were found. These lesions in the intestine agree with the description given by other authors. Bizzozzero found in the solitary lymph nodules and Peyer's patches changes similar to those in the lymph nodules of the spleen and in the mesenteric lymph nodes. The swelling was due to the infiltration of the internodular tissue with lymphoid cells. Oertel found no changes in the epithelium, but necrotic foci were found in the lymph nodules. The changes found experimentally are more marked. Welch and Flexner found in addition to necrotic centres in the lymph nodules a general diffuse necrosis affecting the epithelial cells of the glands. Courmont, Dogan, and Paviot, who injected dogs with the toxin, found hyperæmia and degeneration in Peyer's patches. They think that the intestinal lesions are produced by the elimination of the toxin by the intestine. In addition to these examinations the appendix was examined in 15 cases. The same lesions were found in the lymphoid tissue of this as in the intestine. In two cases an interesting condition not connected with diphtheria was found in the appendix. In one, a child of five years, the appendix in one place was occluded by a mass of mucus, cast-off epithelium, and detritus in which chains of streptococci were found. In the other, a child of ten months, there was a foreign body surrounded by a mass composed of degenerated epithelium, mucus, and bacteria. The bacteria were chiefly the ordinary intestinal bacteria, but in places a few elongated diplococci resembling pneumococci were found. The exact character of the foreign body could not be determined, but it was evidently the remains of a small round parasite, probably an oxyuris vermicularis.

Summary.

The lesions of the small and large in man are relatively unimportant. plasia of the lymphoid apparatus and found in the lymph nodules elsewh

of the lesions does not indicate the action of toxins absorbed from the alimentary canal; they are probably due to the action of toxins from the blood current. There is nothing in the character of the lesions to indicate the elimination of the toxins by the alimentary canal.

LIVER.

The liver in diphtheria has not been investigated with the same care as the other organs, and until recent years some of the most important lesions have been overlooked. The most constant lesion found in the liver by Oertel consisted of small hæmorrhages beneath the peritoneum and in the more superficial part of the parenchyma. He also found a leucocytic infiltration of the subperitoneal and periportal connective tissue, which though varying in extent was never wholly absent. The leucocytes frequently extended from these places into the lobule, separating the columns of liver cells. The lesions in the liver cells were relatively unimportant and consisted of fatty degeneration in the vicinity of the foci of leucocytic infiltration. Katzenstein found cloudy swelling and fatty degeneration of the liver cells, leucocytic infiltration in the periportal connective tissue, and in some cases a tendency to destruction of the nuclei, which stained faintly. In a few cases he found hyaline degeneration of the walls of the capillaries in some parts of the portal spaces and in the peripheries of the lobules. The blood in the capillaries of the liver contained large numbers of leucocytes. Gaston in his treatise on the changes in the liver produced by various infections described in a very general way the changes found in diphtheria, namely, congestion of the vessels, fatty degeneration of the liver cells especially in the centre of the lobules, and infiltration of the portal spaces with embryonic cells. There is embryonic infiltration around the veins, arteries, and bile ducts, and in the latter a catarrhal condition. Macroscopically the liver is enlarged, congested, and contains the "plaques infectieuses" which Hanot described as characteristic of the liver of acute infectious diseases. The plate which Gaston gives shows a

congested liver with nutmeg markings. Barbacci has described the lesions in the liver more fully. He found an abundance of leucocytes in the vessels. The capillaries in places were so greatly dilated that the tissue simulated cavernous tissue, the rows of liver cells between them were reduced to thin masses, and in places they completely atrophied. In the capillaries there were large blocks of stained material which resulted from the breaking down of the blood.¹ The endothelium of the capillaries was often swollen to a considerable degree, and hyaline degeneration of the walls was met with. The liver cells were granular, swollen, and oedematous, and often the cell columns more or less disarranged (*dislocation de la travée hépatique Hanot*). Various degenerative conditions but no actual necroses were found. The lesions in the periportal connective tissue were almost constant and consisted of small cell infiltration which often extended beyond the bounds of the connective tissue and invaded the lobule.

The liver lesions in experimental diphtheria have been much more carefully studied. Babes has given an interesting account of the lesions in the liver, which in several respects agrees with what we have found in man. He found the liver cells swollen, pale, coarsely granular, and in places filled with fat. The lobules occasionally contained small inflammatory foci, and in the vicinity of these the liver cells were more or less separated from their connections. Between the liver cells and in the interior of the capillaries there were mono- and multinucleated leucocytes. The endothelium of the vessels was often greatly swollen and proliferating. The cells coming from this proliferation were large, often exceeding the liver cells in size. They were round or oval, sharply circumscribed, the protoplasm homogeneous, and the nuclei large and irregular. These cells together with leucocytes and granular masses often filled the capillaries. He also speaks of finding groups of pale homogeneous yellow-

¹ This condition described by Barbacci is an artefact due to imperfect preservation of the blood. The tissue of the liver is so dense that hardening agents will only penetrate when very small pieces of tissue are immersed in them. Even then it is advisable to take the sections for microscopic work from near the surface.

ish liver cells without nuclei separated from their connection with one another. Between these there were masses of multinucleated leucocytes, and nuclear fragments derived from the swollen endothelium. The most thorough study of the lesions in the liver produced experimentally is that by Welch and Flexner. The chief changes described by these authors were necrosis of liver cells, affecting usually definite groups, although single necrotic cells were occasionally found. Among the necrotic cells were polynuclear leucocytes which came from the capillaries. The capillaries in and in the vicinity of the necrotic foci contained large numbers of leucocytes, and often swollen and desquamated endothelial cells. Baldassari paid particular attention to the changes in the nuclei. He found the changes most marked in those cases in which the infection took a longer course. The liver cells showed cloudy swelling, fatty degeneration, and necrosis; the necrotic cells formed foci chiefly in the vicinity of the central vein. In places the necrosis was so advanced that the structure disappeared, and in the area there was only cell detritus composed of albuminous granules, altered nuclei, and emigrated leucocytes. The most characteristic changes in the nuclei consisted of fragmentation of the chromatin network; the chromatin masses separated from their connection and formed a circle around the nuclear membrane. The whole chromatin network might break down, and the nucleus become diminished in size and stain intensely. In other cases the nucleus contained no chromatin network, and appeared as a vesicle. Sometimes the nuclear membrane broke up and particles of the chromatin appeared in the cytoplasm. In the most severe cases not only was there no chromatin, but the nucleolus was not visible. He quotes the work of Trambus to the effect that the nucleolus is more resistant than the chromatin; and where it has disappeared this denotes a more intense action of the injurious substance. The only other agents which he found to produce results comparable to those in the diphtheria were arsenic and phosphorus.

The recognition and the interpretation of the lesions in

the liver presented great difficulties. This was not due to the complexity of the structure, but to the closeness of the texture; so many different elements, which, especially in a degenerated condition, may closely resemble one another, are so close together. The ordinary paraffin sections proved totally inadequate, and it was only after securing, by means of the Blake-Minot microtome, sections $2\ \mu$ in thickness, and by the application of special means of staining that it was possible to explain some of the conditions met with. The tissue was hardened in the usual way in Zenker's fluid, and only those cases were examined in which the preservation was good. The stain found most useful was the connective tissue stain of Mallory. The especial advantage of this was that it differentiated clearly the walls of the capillaries, and showed the structure of the cytoplasm much better than any other that we used. The presence of necrotic foci could most easily be distinguished under a low power in sections stained with methylene blue and eosin, or hæmatoxylin and eosin, because the eosin stains the necrotic cells intensely. The liver was examined in 180 cases, these embracing cases of all ages and of all stages of duration of the disease. The character and extent of the lesions varied greatly, and did not seem to depend, to any degree at least, upon the duration of the disease. In a general way, however, certain lesions were more marked in the more acute cases, and others in those of longer duration. The liver did not present any characteristic macroscopic appearance. Generally it was slightly swollen, somewhat tense, and congested. In some cases the congestion was marked and a considerable amount of blood flowed from the cut surface. Frequently the congestion was irregular; there were pale, slightly yellowish foci from one to several cm. in diameter in the dark red tissue. In some cases the liver was pale chiefly to the extent of the fatty nothing in the macroscopic appearance of the liver in diphtheria from the liver in infectious diseases.

On microscopic examination th

swelling of the cells with increased granulation. This affected all portions of the lobule, but was rather more marked in the centre. In specimens stained with the triple (connective tissue) stain the cell boundaries were sharply outlined, due to the staining of the bile capillaries, which are refractive and take a distinct brownish-red color. The normal cell is indistinctly granular, and there is a fine reticulum to be made out extending throughout the cell protoplasm. In what we regard as the slightest form of degeneration the reticulum is more evident and actual spaces in the cells can be seen. (Plate XXIII., Fig. 2; Plate XXII., Fig. 2.) These spaces probably are due to increase in the intracellular fluid. They are totally different from the distinctly round and sharp-cut outlines of the cavities due to fatty degeneration of the cell, remaining after the fat has been dissolved out. In places the capillaries are compressed by the swollen cells, in others they are wider than normal. With this oedematous condition of the cells there is often combined a change in the granulation. The granules become more prominent and vary in size and in staining. The reticulum of the cytoplasm becomes less evident or invisible. In place of the fine, even granulation of the normal cell, coarse granules of irregular size appear, some of them staining a deep brown in the triple stain. In some of the swollen cells this granulation is extremely evident, owing to the disappearance of the intracellular network. In certain of the sections stained with methylene blue there are granules in the protoplasm which take the blue stain with varying degrees of intensity. Some of these are of regular size and often arranged in pairs or short series resembling micrococci or short bacilli. In most cases the stained material is of irregular size and stains indistinctly. Similar stained masses were found in the specimens stained with hæmatoxylin, but they were not so evident. In two of the cases, both of them acute, granules of varying size staining more distinctly than the other granules in the cell were found enclosed in definite vacuoles. They were very similar to the inclusions found in the epithelial cells of the kidney in one of the cases, and also similar to some of the inclusions found in

carcinoma cells. A definite hyaline degeneration of the protoplasm resulting in the formation of hyaline globules was found in but one case and in but a few cells in this. The hyaline droplets stained blue in the triple stain just as did the hyalin in the kidney epithelium. This form of degeneration is certainly rarer in the liver than in other glandular organs. This degeneration of the protoplasm in most cases takes place without any change in the nucleus. An apparently normal nucleus was often found in cells in which there were marked changes in the protoplasm. In several cases a peculiar change in the nucleus was found which has been described by several authors (Barbacci, Katzenstein, Baldassari). In this condition the nucleus becomes greatly enlarged and vesicular. The chromatin disappears entirely from the interior of the nucleus and becomes arranged around the periphery, making the nuclear membrane more conspicuous. The nucleus then appears as a large, conspicuous vacuole in the cell, and within it, usually at one side, clinging to the nuclear membrane, is a very small unstained vesicle which we have regarded as the altered nucleolus. This form of degeneration of the nucleus of the liver cell is comparatively rare and it is not confined to diphtheria. We have found a great number of nuclei so altered in the liver from a case of leucæmia. The vesicular nucleus is not always round, but may be bent or folded on itself in a variety of ways.

It was very difficult to judge of the presence and degree of fatty degeneration. A varying number of fat vacuoles were found in the cells. Some of these were large, others very small. The large fat vacuoles were more commonly found in cells in the periphery of the lobule, and the smaller were more evenly distributed. In some cases almost all the cells were filled with very small fat vacuoles. There was no relation between the amount of fat present and other degenerative conditions of the cells, and a similar distribution of fat may be found in the livers of children dying from various diseases.

The most extensive degeneration consisted in actual necrosis of the liver cells. The necrosis was always more

marked in the vicinity of the hepatic veins than elsewhere. The necrosis was never diffuse affecting scattered cells, but was always found in groups of cells. (Plate XXIII., Fig. 1.) Two distinct forms of necrosis could be distinguished. In one, the more common form, it affected the cells around the central vein. From this it extended a variable distance towards the periphery. In the specimens stained with methylene blue and eosin the necrotic foci could be easily distinguished even with a low power by the more intense staining of the necrotic cells with eosin. In the triple stain they stained darker than the other cells. Apparently various stages of the necrosis could be distinguished. The totally necrotic cells were homogeneous, hyaline, and refractive. They were small and had lost their typical shape and their connection with one another, appearing as irregular masses lying loosely in contact. (Plate XXIII., Fig. 3.) There was no appearance of the nucleus in these cells, and no nuclear detritus. Where the necrosis was not so far advanced the cells were larger, contained more granules, and the nucleus could be distinguished, though it had undergone various changes. In some cases the nucleus seemed simply to disappear; in others the chromatin became swollen, forming a homogeneous mass which in some cells stained intensely. The chromatin seemed to undergo the same hyaline degeneration as the protoplasm and never broke up into fragments. In most cases this central necrosis occupied the entire centre of the lobule; in others it appeared only at a small point, the remaining cells being unaltered, and from this extended a short distance towards the periphery. The very considerable space separating the rows of liver cells in these foci was very striking. Barbacci has called attention to this and regarded the degeneration of the cells as due to pressure exerted by the dilated capillaries which filled the space between them. Examination with low power of specimens stained with methylene blue and eosin seems to show this, but high power examination of very thin specimens stained with the triple stain shows a very different condition. This stain brings out sharply the capillary wall and shows that the altered liver

cells lie in a wide space between the capillaries. (Plate XXIII., Fig. 3; Plate XXII., Fig. 3.) On either side between the degenerated liver cells and the capillary walls there is a space which is filled with granular debris apparently resulting from the destruction of the cells and from the coagulation of the exudation. The granular material is very irregular in size and most of it is colored by the orange stain in the mixture. When the liver cells are entirely separated from their connection they lie as a loose mass in the space among the granular debris. Clear orange-stained vesicles similar to those so commonly found in the tubules of the kidney were occasionally found in the space lying among the debris. (Plate XXII., Fig. 4.) The capillaries instead of being dilated are actually compressed and in places totally obliterated. They contain a variable number of red corpuscles which are also sometimes found in the intercapillary spaces with the other material. In most cases the necrosis is confined to the centres of scattered lobules; in others almost all the lobules in the section are affected. One remarkable fact about these central necroses was the rarity with which they were invaded by other cells. In most cases the spaces were entirely occupied by the necrotic cells, granular debris, and an occasional red corpuscle. In other cases a very few polynuclear leucocytes which generally showed some nuclear degeneration were found, and occasionally an endothelial cell. Nor did the capillaries either in the necrotic foci or surrounding this contain an unusual number of leucocytes. We have regarded the formation of this space around the capillaries as due in part to exudation and in part to the shrinkage of the cells forcing the intracellular fluid from them. The main element, however, in producing the condition must be exudation through the capillary walls. It is not a process secondary to the necrosis, for it was found in places where there was no necrosis, though it was more marked in the central necrotic foci than elsewhere.

The disseminated foci of necrosis were not so common as the central necroses, and in a number of ways differed from them. They were found in but 7 of the 180 cases, while the

central necroses were found in 22. The two processes were but rarely found associated together. The disseminated foci varied in size from those containing but few cells to those forming a considerable part of the lobule. (Plate XXIII., Fig. 1.) They were much more difficult of interpretation than the others, owing to the greater number of cellular elements contained in them. The necrotic liver cells presented about the same appearance as the necrotic cells in the central necroses. Like these they were more or less broken down and separated from their connection with one another, and lay in spaces between the capillaries, though the spaces were not so large. Among the necrotic cells in the spaces there were almost invariably numerous other cells. These were in part polynuclear leucocytes, with the nucleus in some cases well preserved, in others fragmented. These lay between and in some cases within the necrotic cells. Among them were other cells, with large irregular vesicular nuclei, which were similar to the cells, evidently of endothelial origin, which were found within the capillaries. In some foci all these cells could be distinguished as such; in others they were so degenerated that only fragments of cells and nuclear detritus appeared. The capillaries were difficult to make out. They contained very few red corpuscles, a variable number of leucocytes and endothelial cells, and almost invariably some fibrin. The capillary walls were frequently thickened and hyaline. The obstruction of the capillaries was due only in part to the œdema, but chiefly to the cells and fibrin. In one case small foci were found which could almost be regarded as minute abscesses. In these foci the capillaries were filled with polynuclear leucocytes, and such numbers of them were found in and among the necrotic cells that the details of the lesion were obscured. In no case did either of these forms of necrosis seem to be entirely due to an injurious agent affecting the liver cells primarily.

These circumscribed necroses met with in the liver have attracted much attention and their pathogenesis has been obscure. A very diffuse form of necrosis apparently not connected with bacteria was described by Councilman in

yellow fever. The necrotic cells were invaded by leucocytes. Subsequently Councilman and Lafleur described necrosis of the central cells of the lobules in amœbic dysentery, and regarded it as due to the action of toxins absorbed from the alimentary canal. Reed regarded the nodules found in the liver in typhoid fever and generally described as typhoid lymphomata as due to primary necrosis of groups of liver cells with subsequent invasion by polynuclear leucocytes. Mallory subsequently showed that these foci were due to capillary occlusion, and that the cells found in the capillaries and among the necrotic liver cells were chiefly or entirely endothelial in origin. Barker described necrotic foci in the liver in malaria. There were numerous thrombosed capillaries in the necrotic foci, and Barker was inclined to regard the necrosis as secondary to the capillary thrombosis.

Flexner, who has given the most complete description of the necroses in the liver produced in experimental diphtheria, regards the necroses as due to injury of the wall of the vessel at some point allowing transudation to take place more freely. He supposes that the injury is produced at some period of greater concentration of the toxin and at a point where the circulation is slowed or at a standstill. He very properly rejects the theory that the necrotic cells represent cells of less resistance which succumb to the action of the toxin. It seems possible that such a theory might explain the very diffuse necroses in yellow fever, but it is impossible to apply it to groups of cells. Although Flexner rejects the theory of less resistance the theory he advances is almost as hypothetical. It is impossible to compare the necroses met with in the human liver in diphtheria with those produced experimentally. The livers both of rabbits and of guinea-pigs are much more susceptible to necrosis than the human liver, and necroses are found in them in a great number of infections. The most common of the necroses in man, that around the central vein, is rarely found in these animals; the necroses in them take the disseminated form. We are inclined to regard both forms of necroses, both that around the central vein and the form in disseminated nodules, as due

to capillary obstruction plus the action of the toxic substance. The main factor in the production of the central necrosis is capillary occlusion due to the pressure exerted by the exudation. Occlusion of the capillaries by thrombi also plays some part. Though exudation is more marked in the central necrotic area it is not confined there. The fact that the necrosis takes place in the centre and not in the periphery may be due to the fact that the circulation in the periphery may be maintained by the capillaries in the periphery discharging into those of adjacent lobules. The disseminated necroses are almost certainly due to capillary obstruction brought about by fibrin (Plate XXII., Fig. 4), by endothelial cells (Plate XXIII., Fig. 4), and by leucocytes, either singly or combined. In one case necroses were found which were very similar to those found in typhoid fever. There is nothing characteristic about these diphtheria necroses. They are found in the same form and in almost as great numbers in other infectious diseases. They sometimes very closely resemble miliary tubercles. In the most acute form of miliary tuberculosis of the liver there is necrosis of the liver cells and accumulation of endothelial cells in the capillaries, but the formation of the latter is due chiefly to the tubercle bacilli enclosed in them.

Apart from the lesions in the capillaries which we have described in connection with the necroses there are few other changes in these vessels. The walls of the capillaries are often swollen and hyaline in the necrotic foci, and occasionally a slight degree of this change is found elsewhere, but we have never found any extensive hyaline degeneration such as Barbacci has described.

In the examination of the liver our attention was early attracted by the number and character of the cells in the vessels. It has seemed to us that in the normal liver there are few leucocytes in the capillaries, fewer than in the capillaries of other organs. Almost all observers have described increased number of leucocytes in the capillaries and veins of the liver in diphtheria. It is true that the number of cells is increased in almost all cases and in some greatly so.

Comparatively few of these are polynuclear leucocytes, except in the vessels within and in the vicinity of the foci of necrosis. The most numerous cells found are the varieties and derivatives of the lymphoid cells, the small and large lymphoid cells, and the plasma cells. We have never found this accumulation comparable to that met with in the vessels of the medulla of the kidney. The next most numerous cells are large cells derived from proliferation of the endothelium of the vessels. These are found both attached to the wall and free in the lumen. They have a vesicular, often distorted nucleus and pale homogeneous protoplasm. The cells vary greatly in size. Some of them are so large that they extend along the capillary a distance of the diameter of 4 or 5 liver cells; others are no larger than the ordinary leucocyte. These cells have marked phagocytic properties and they often contain cell inclusions. The included cells are chiefly lymphoid cells and red blood corpuscles. Polynuclear leucocytes are rarely found within them. The nuclei of the included lymphoid cells are often fragmented and the cell contains the peculiar nuclear detritus to which these cells give rise. The protoplasm of the endothelial cells is often degenerated, contains numerous vacuoles, and an occasionally hyaline droplet. We have never found any bone marrow cells in the liver capillaries. Particular attention was directed to the search for parenchymatous emboli of liver cells. These were never found in the examination of the lung and other organs, and it would seem as though the central necroses with disruption of the liver cells should have given rise to them. In the larger vessels single liver cells and adherent masses of these were frequently found. They were found, however, fully as often in the portal as in the hepatic veins, and in our microscopic examinations of the liver in all sorts of diseases they were often found. We have regarded these cells, particularly the masses of them, as artefacts; in the cutting of the fresh tissue the liver cells must often be forced by the knife into the larger blood vessels. Similar conditions are often found in the kidneys, where single epithelial cells or adherent masses are contained in the large

veins. Cells which could be recognized as liver cells were never found in the capillaries; but we do not think it would be possible to distinguish a degenerated liver cell in a capillary from a degenerated endothelial cell.

Hæmorrhage was rare, and was found in a marked degree in but two cases. In the central necroses single red corpuscles were often found in the pericapillary spaces. In the two cases in which the hæmorrhage was marked there was considerable congestion, particularly in foci, and in some of these the red corpuscles were closely packed in the pericapillary spaces, and between the liver cells. No rupture of the capillary walls could be made out in these places, the hæmorrhage having probably taken place by diapedesis.

There was often a marked degree of cellular infiltration around the portal spaces, and these were increased in size. The cellular infiltration was more marked in the chronic than in the acute cases. The infiltrating cells were chiefly lymphoid and plasma. In a few cases the cellular infiltration extended from the portal spaces into the lobule, and in some cases was undoubtedly accompanied by connective tissue formation.

No diphtheria bacilli were found in the liver on histological examination, and in but one case were emboli of micrococci found, and in this case there were no lesions in the liver cells around them.

Summary.

The lesions produced in the liver in diphtheria are not characteristic, and do not differ from those found in other acute infectious diseases. They are due to the effect of soluble toxic substances, and not to the presence of diphtheria bacilli. The most common lesions are a general degeneration of the liver cells, and necroses which are chiefly found in the centres of the lobules. It is probable that the disturbance of the circulation without the injury produced by the toxin would be insufficient to produce necrosis. Slight hyaline degeneration of the capillary walls is occasionally found, and the capillaries constantly contain an increased number of cells, which are partly produced by proliferation

of the endothelium, and partly brought to the liver by the circulation. The lesions in the human liver differ from the lesions produced experimentally in guinea-pigs and rabbits by the diphtheria bacilli or toxin chiefly in the greater frequency of the central situation of the necroses.

KIDNEYS.

The literature on the anatomical changes in the kidneys in diphtheria is not extensive. The article of Brault is the first which is devoted exclusively to the renal lesions produced in diphtheria. He found the kidneys hyperæmic, the vessels of the glomeruli dilated, and blood and epithelium in the capsular spaces. The chief change consisted in degeneration of the epithelium of the convoluted tubules, and this was more marked in diphtheria than in other infectious disease. The endothelium of the vessels was often swollen and projected into the lumina. Fürbringer, who examined the kidneys in 10 cases, found intense parenchymatous degeneration of the epithelium of the labyrinth with desquamation, no changes in the glomeruli, and in a few cases an interstitial cellular infiltration. Fischl found interstitial cellular infiltration around the vessels, swelling and degeneration of the epithelium of the glomeruli, and hyaline masses in the capsular spaces. Tschiglow investigated 17 cases and found degeneration of the convoluted tubules in all and lesions of the glomeruli in six. Oertel devotes considerable attention to the lesions in the kidneys and gives a very good description of the interstitial changes. Hæmorrhages were constantly found beneath the capsule and but rarely in the parenchyma. Foci of cellular infiltration consisting of large and small round cells were frequently found beneath the capsule, around the vessels and glomeruli, between the tubules in the upper and deeper layers of the cortex, and around the small arteries of the pyramids. The cells in the foci seemed to be only in small part formed by proliferation of the connective tissue cells. The changes in the glomeruli consisted of hæmorrhage, exudation into the capsular space, and degeneration of

the capillaries. He describes as a peculiar form of degeneration the appearance of a striated border on the cells in the convoluted tubules. He believed that this condition, regarded by Lorentz as normal, was due to degeneration and partial destruction of the protoplasm laying bare the rod-shaped structures which Heidenhain had described in the epithelial cells. Kuck in an article on albuminuria in diphtheria says that in spite of the albuminuria the changes found at autopsy are chiefly negative. Bernard and Felenthal found extensive lesions in the convoluted tubules consisting of granular and hyaline degeneration. Casts, generally hyaline, were found in all cases. Hæmorrhages were commonly found. Changes in the glomeruli were not common, but in several cases the capsular epithelium was swollen and granular. In all of the 24 cases investigated foci of cellular infiltration were found in the interstitial tissue. Reiche found in all cases examined degeneration of the epithelium, in a few cases lesions of the glomeruli. In a number of cases there was inflammatory proliferation of the connective tissue, and in three cases interstitial round cell infiltration in the pyramids. Katzenstein found degenerative changes the most common lesion, and interstitial changes only in the most severe cases. Flexner in the experimental lesions of diphtheria found hyaline thrombi frequently in the vessels of the glomeruli, and degeneration and necrosis in the tubules. Councilman¹ found interstitial changes in the kidneys in 24 out of 103 cases of pure diphtheria, and in 5 out of 23 cases of mixed infection of diphtheria with scarlet fever.

The kidneys were examined microscopically in 171 cases. Only those cases were excluded from microscopical examination in which the tissue was imperfectly preserved. The usual method of hardening in Zenker's fluid and cutting the sections in paraffin was followed. The Blake-Minot microtome was found extremely useful in preparing very thin sections for examination with high power. As a matter of routine the sections were stained in methylene blue and eosin,

¹This material is also included in the present article.

in hæmatoxylin and eosin, and in plain hæmatoxylin. In studying the degenerations the connective tissue stain of Mallory gave excellent results.

In a number of cases serial sections were made in order to find in just what part of the course of a tubule certain changes occurred. In this study of serial sections we were greatly aided by photography. The ages of the cases ran from two months to thirty years; the general average was three and three-fourths years. In the examination of so large a number of cases of the kidneys of children there were certain anatomical points brought prominently to our notice. It is known that the glomerulus of the newly-born child differs widely from the glomerulus of the adult. The difference is shown in the small size, the simpler structure, and the very evident covering epithelium in the glomerulus of the child's kidney. This type of glomerulus is gradually lost. There is very little difference in structure between the glomeruli in a child of two months and the newly born. The adult type is not reached before four years, and there seems to be a gradual increase in size of the glomerulus up to ten or twelve years. This gradual growth of the glomerulus is so well marked that under seven years it is possible to tell the age with considerable accuracy from the examination of the kidneys. Not all the glomeruli in the child's kidney show the same stage of development. Glomeruli corresponding perfectly to the embryonic type consisting of a few vascular loops covered with high epithelium were found up to seven years of age. Their number varies greatly in different cases. They are almost always present up to two years and after this they may or may not be present. They are confined almost exclusively to the tissue just beneath the capsule, but they may be found elsewhere. None of the cases enables us to say whether these embryonic glomeruli were more numerous adjoining losses of substance, nor was it possible to say what part they played in the pathological conditions of the glomeruli, for they were not present in any of the cases marked by glomerular lesions. No attempt was made to trace the relation of these embryonic glomeruli to the tubules.

From the microscopic examination it was found possible to divide the kidneys examined into five groups: 1. Those in which degeneration of the epithelium was the chief or the only lesion. (Plate XXIV.) 2. Those in which acute interstitial changes, consisting of cell accumulations in the vessels and interstitial tissue, were present. (Plate XXV., Figs. 2 and 3.) 3. Those in which the chief lesions were found in the glomeruli. (Plate XXVI.) 4. Those in which hæmorrhage into the tubules was present. 5. Those in which chronic interstitial lesions were present as shown by atrophied glomeruli and increase in the connective tissue.

1. *Degenerative changes.* — There is a great deal of difficulty in the determination of slight degenerative lesions in the kidney. The epithelium, particularly of the convoluted tubules, changes rapidly after death. Differences in mode of hardening and staining lead to differences in the appearance of the tissue. Even extensive desquamation of the epithelium may be found as the result of post-mortem change. The normal epithelium is very granular and differences in the degree of granulation and in the size of the cells are difficult to determine. It is often more easy to determine slight degrees of degeneration from the general aspect of the tissue under a low power than by a more detailed examination under high powers. The convoluted tubes are easily distinguished from the other tubes by their course and the character of the epithelium. The upper portion of the ascending loop of Henle has epithelium similar to the distal convoluted tube. We shall speak throughout of the convoluted tube which passes from the glomerulus as the proximal convoluted tube, and the convoluted portion which is the continuation of the ascending loop of Henle as the distal convoluted tube. There is considerable uniformity between the structure of the epithelium in these two portions of the tubule. In both the epithelium is granular. The granules are distinct, they vary somewhat in size and in intensity of staining. They appear to be enclosed in a meshwork; at least a more or less indefinite reticulum can be distinguished in the cases of degeneration in which the contents of the cells

have been in great measure lost. There is nothing corresponding to the rod-like structures described by Heidenhain. Toward the bases of the cells there is some tendency for granules to arrange themselves in rows perpendicular to the base. The rows of granules somewhat simulate the appearance of rods. The cells terminate towards the lumen by a ciliated border.

The cilia are relatively short compared with cilia in other situations, but are perfectly distinct, and in good preparations the separate cilia can be distinguished. (Plate XXIV., Fig. 2.) They are not easily lost, and they are present in places even when there is a considerable degree of degeneration. In sections stained with Mallory's connective tissue stain they are darker than the cell protoplasm. Often when the cilia cannot be distinguished the border of the cell has a rather indefinite darkish color due to the adhesion of the separate rods. (Plate XXIV., Fig. 1.) These cilia spring from a sharp border of the cell in which there is a row of small granules which stain in the same way as the eosinophile granules, and which can be distinguished by their bright color and situation from the other granules in the protoplasm. The cilia apparently terminate in this granular border, but we were not able to make out with certainty any connection between the cilia and the granules. In some cases it seemed possible to follow the cilia into the cell protoplasm beneath the granules, but this was probably due to imperfections in the sections. Certain conditions in the tubules will make the cilia more apparent. They are most easily seen when the lumen is large. They are found in normal kidneys, and in all possible pathological conditions, but fresh tissues are necessary for their demonstration. It is not possible to make out any of the fine structures of the kidney epithelium when the autopsy is more than a few hours after death, unless the body has been kept at freezing temperature. The cilia are found only in the ascending loop of Henle, and in the convoluted tubules. In the latter they are much more evident in the distal than in the proximal tubule. The difference is so marked that we were at first inclined to consider them absent

in the proximal tube, but we have in a few cases undoubtedly found them in this situation.

In a number of cases the tubules of the cortex contained number of vesicles. They varied in size, and when few were present they were round; when numerous they were pressed closely together, and their edges formed a reticulum. They were either empty, or contained a few granules which were generally larger and less brightly stained than the granules in the protoplasm. The envelope of the vesicle was usually thin and smooth, but occasionally granules were adherent to it. The vesicles were not found except in the cortex of the kidney, in the convoluted tubules, and in the ascending loop of Henle. The envelope of the vesicles and the granules contained in or adherent to it stain with eosin and with fuchsin; with the connective tissue stain of Mallory they take a decided yellow color due to orange G. We are not able to say anything about the character and origin of these vesicles. They are usually very well marked in the kidneys from cases of acute infectious diseases; they may be present along with evidences of degeneration, or in kidneys apparently normal. In this large series of cases presenting every form and degree of degeneration the condition was not common; but in the kidney obtained from a young woman (who committed suicide by stabbing) and used as a normal type for comparison, these vesicles were extremely well marked. In other normal kidneys they were not present. These vesicles have been considered as drops of secretion coming from the cells as evidences of cell degeneration (in this case the vesicles are supposed to represent sections of the ends of the swollen vesicular cells), and as formed from the coagulation of albumen. None of these explanations seem to us sufficient. Were they actually drops of secretion, they should be seen well in the cells as in the lumina of the tubules; they were not present in the cases in which the epithelium was swollen and vesicular, and we have never found the coagulation of an albuminous exudation in any situation to give such an appearance. That it is not peculiar to the kidney is shown by our finding a similar appearance in other situations, as in the

bronchi behind the epithelium, which was raised from the surface, and in similar relation to the gastric and other epithelia.

Degenerative changes varying in character and extent were found in 112 of the 171 cases examined. Macroscopically these kidneys differed but little from the normal. The degree of congestion varied; in some cases the kidneys were slightly swollen, the cut surface more opaque, and the markings obscure. A considerable degree of degeneration may be found in a kidney which presents a perfectly normal appearance to the naked eye. According to the degree of degeneration the cases were divided into those with slight degeneration, 26 cases; those with a medium degree, 38 cases; those with a marked degree, 37 cases; and those with an extreme degree, 9 cases. The most extreme degree was found in those cases of severe type which died shortly after their entry into hospital. The average duration of the 9 cases was four and one-half days, and of all the cases of degeneration seven and one-half days. Fatty degeneration as determined by frozen sections was usually only slight in degree. It was found, however, in 44 out of 58 cases which were examined for it. The slightest form of degeneration shown in the hardened sections consisted of swelling and irregularity of form of the cells with an increase of the granular contents. The granules were often larger or smaller than normal and the increased size of the cells seemed to be due more to increased size of the granules than to an increase in their number. (Plate XXIV., Fig 1.) In places the part of the cell adjoining the lumen was swollen, pale, and contained very few granules. The outlines of the altered cells in many cases were sharp and the ciliated border perfectly preserved. (Plate XXIV., Fig. 2.) In other places the cells were ruptured and their granules escaped into the lumina of the tubules. The granules were often found in tubules in

ing entire fragments of cells were found. In places tubules could be found entirely filled with a mass of granules and cell fragments. The process of cell destruction was often very apparent in tubules in which the cells were represented by only a small mass of granular material around the nucleus, and in places no trace of the cells could be made out. With this change in the cells, consisting of simple destruction, there was often combined a more advanced form of degeneration consisting of a change in the character of the cell contents. Among the granules certain ones could be distinguished by their larger size, and less degree of refraction. These larger granules stained in some cases as the other granules of the cells, or were somewhat paler. As they increased in size they gradually assumed with the Mallory connective tissue stain a deep blue color, similar to that of the connective tissue. Only single scattered blue globules were found in the cell, or the entire cell was filled with them. (Plate XXV., Fig. 1.) They varied in size from those no larger than the cell granules to large masses twice the size of the nucleus. Finally the cells ruptured and the hyaline globules filled the lumen of the tubule. Some degree of this hyaline degeneration was found in almost all the cases, even in those in which the lesions were very slight. In some cases it was most marked and some degree of it was found in almost all the proximal convoluted tubes. It was most evident in the degeneration which occurs in connection with the glomerular affections. It was much more evident in the proximal than in the distal convoluted tubules and in that portion of the tubule nearest the glomerulus. In one case in which serial sections were cut it was possible to trace the hyaline degeneration to the beginning of the tubule, and in this case the glomeruli were not affected. The nuclei in many cases were unaltered even when a high degree of degeneration was present. (Plate XXIV., Fig. 1.) But in some cases they also showed pathological conditions consisting of swelling and loss of chromatin, or the whole nucleus was converted into a faintly staining homogeneous mass somewhat resembling a hyaline globule. In several cases the cells

were greatly swollen, filling entirely the lumina of the tubules. In these swollen cells there was a more or less definite reticulum enclosing scattered granules of various sizes. (Plate XXIV., Figs. 3 and 4.) Extreme degrees of degeneration could be present without any formation of hyalin in the cells.

In one case a form of degeneration was found which we have never seen before. In this case, along with a general high degree of degeneration, vacuoles were found in the cells containing round, generally granular masses. These masses varied somewhat in size, and they were usually found in the peripheral part of the cell. The nuclei, though often degenerated, were generally present in the cells containing the enclosures. It was impossible for us to determine the exact nature of these enclosed masses; they certainly did not seem to be enclosed cells, for they varied too much in size and contained no chromatin fragments. They appeared rather to be masses of protoplasm separated from the remainder of the cell. In one place there was a double inclusion: a small mass lying in a vacuole itself contained a vacuole and a small included body. The included bodies were only found in the cells of the convoluted tubules and the ascending loop of Henle. The case was that of a child five years old who died on the seventh day of the disease.

The degree of degeneration varied not only in the different tubules, but in different parts of the same tubule. This was particularly true of the hyaline degeneration. Desquamation of epithelium was not marked. Occasionally the tubules of the pyramids contained single epithelial cells and adherent masses of them, but usually the cells seemed to go to pieces gradually rather than to be lost as a whole. Casts were practically always present. They were most numerous in the cases with
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which are found in the urine in these cases are formed from degeneration and destruction of cells. It is also true that this is not the only source of the cast, for in some of the cases of glomerulo-nephritis the tubules contained a considerable amount of fibrin.

The most constant change found in the glomeruli consisted of a small amount of granular coagulum between the tuft and the wall. In cases of marked hyaline degeneration of the tubules, this change extended to the epithelium of the capsules and the cells were swollen and contained hyaline droplets. The degeneration was rarely associated with any cellular exudation. In one case of mixed infection of diphtheria and measles large numbers of polynuclear leucocytes were found in the tubules and in the vessels. In this case both diphtheria bacilli and staphylococci were found in cultures made from the kidneys.

There are records of the examination of the urine in 40 of the cases of simple degeneration. So many of the cases were in very young children who were brought into the hospital in a moribund condition that the systematic examination of the urine was a matter of great difficulty. Albumen was present in 33 of the 40 cases. As a rule the examination was made in the cases of longer duration. While there was some general agreement between the presence of albumen and the degree of degeneration, there were some exceptions to this; in one case no albumen was found where marked degeneration existed, and in another a large trace was found with very slight degeneration. In two of the cases there is a note of complete suppression for twenty-four hours. In the few microscopic examinations of the urine which were made there were granular and hyaline casts.

The mixed infections were less common in the cases which showed degenerative lesions than in the cases with more severe lesions. In the degenerative cases mixed infections were more frequent according to the severity of the lesion. In the 26 slight cases there was no scarlet fever and but 1 case of measles; in the remaining 84 cases there were 11 of scarlet fever and 5 of measles. There seemed to be no

relation between the character of the degeneration and general infection with various bacteria. In the 110 cases a general infection with the diphtheria bacillus was found 20 times, with the streptococcus 29 times, and with the staphylococcus aureus 4 times; with the pneumococcus 3 times. In 9 cases in which the degeneration was most extreme there was a general infection in but 1 case and that with the streptococcus. Bacteria were found in the cultures from the kidney in 61 cases. In this group of cases also there was no relation between the extent and character of the lesions and the presence or the character of the bacteria.

2. *Acute interstitial changes.* — In 43 of the cases acute interstitial nephritis was present. (Plate XXV., Figs. 2 and 3.) We have included under this head all of the cases in which the interstitial tissue of the kidney was infiltrated with cells of the plasma variety. In the most marked cases of this lesion the kidneys were greatly enlarged. In one case of combined diphtheria and measles in a child of two years the combined weight of the kidneys was 480 gms., and in two other cases, one a child of five years, the other a child of two and one-half years, the kidneys weighed respectively 250 and 225 gms. This extreme enlargement, which may be more than four times the normal, is rare; the kidneys usually are little if at all enlarged. In the cases of great enlargement the capsule is distended, thin, and often separates spontaneously on section; the foetal markings are less distinct and often obliterated, and the surface is pale, of a grayish opaque color, mottled, with irregular, more hyperæmic areas. The stellate veins of the surface are enlarged, and punctiform hæmorrhages are often found in their vicinity. On section the normal markings are obliterated and the contrast between pyramids and cortex is less distinct. The increased size is chiefly due to the swelling of the cortex. In the less marked cases there are opaque areas often in lines corresponding to the course of the tubules and due to the interstitial infiltration. In the most marked case, in which the two kidneys weighed 480 gms., the interstitial infiltration was so intense that the tubules were masked by it. (Plate XXVI., Fig. 3.) It

was general in all parts of the kidney, but was more intense in foci; groups of tubules were often found with but little infiltration between them. Most of the cells in the interstitial tissue are plasma cells with typical nucleus and protoplasm. In the most extreme case there were numerous polynuclear leucocytes among them and some of the tubules were filled with them. In this case there were also numerous large phagocytic cells which often contained plasma cells, lymphoid cells, or polynuclear leucocytes lying in vacuoles. These phagocytic cells were rarely seen in any of the other cases. Lymphoid cells were numerous, and also cells which seemed to represent a transition between these and plasma cells. The focal character of the infiltration was well marked. The foci were most numerous at the base of the cortex adjoining the pyramids, just beneath the capsule, and around the glomeruli. In some cases the foci were confined to the pyramids. Polynuclear leucocytes may or may not be present. They were found both in the tubules and in the interstitial tissue, and there seemed to be some relation between them and the degree of degeneration of the epithelium. The degeneration of the epithelium varied in the different cases and in different foci in the same kidney. In some places there was little or no degeneration, and a marked degree of interstitial infiltration was often found between tubules which presented a perfectly normal appearance. In other cases the tubules in the interior of the interstitial foci showed a marked degree of degeneration and in some cases actual necrosis.

The infiltrating cells were usually confined to the interstitial tissue. Occasionally a few cells similar to them were found in the tubules themselves, especially where these were degenerated. Nuclear figures were found in variable numbers in the cells in the interstitial tissue. In no case were they wholly absent. These changes in the interstitial tissue are always accompanied by changes in the vessels. The infiltrating cells are found in the vessels as well as in the tissue, and they may be so crowded together that it is difficult to distinguish the vessels. Most of the cells in the vessels have the same character and the same peculiarity of staining as

the cells outside. Nuclear figures were found in these cells, but in no such numbers as in the cells outside the vessels. Very few polynuclear leucocytes were found in the vessels along with these cells. The numbers of cells in the vessels were not always proportionate to the degree of interstitial change. Sections in which the vessels were blocked with cells might show but slight interstitial change, and occasionally interstitial foci are found where but few cells could be made out in the vessels.

Particular attention was paid to the vessels in the examination of all the sections. Cell accumulations were found in the vessels in a large number of cases in which degeneration was the only lesion. The cells were found in greater numbers in the small veins in the upper part of the pyramids than elsewhere. In certain cases they were so numerous that the vessels were apparently blocked by them. Such cell collections were occasionally seen in the stellate veins of the cortex and elsewhere, but in most cases they were confined to the veins of the pyramids.

Most of the cells in the vessels had the same general character as those in the interstitial tissue. Others resembled closely the large granular cells of the bone marrow, and in a number of cases, representing all forms of lesions, the large cells of the marrow were found in the capillaries of the glomeruli, but they were never so numerous as in the capillaries of the lungs. In some cases only lymphoid cells were found in the vessels. Polynuclear leucocytes were extremely rare among them. In some cases a few might be found, but in most cases it was possible to examine all the vessels in the pyramids without finding any. The presence of the cells in the interstitial tissue does not seem to be in any degree dependent upon the degeneration of the epithelium. The most advanced epithelial degeneration was found in cases in which no cells were present, and as we have said marked interstitial changes were found without degeneration. The degeneration found in foci of intense infiltration seems to depend on this infiltration, and be due to malnutrition produced by the blocking of the vessels.

In all of the interstitial cases the duration of the illness was more prolonged than in cases of simple degeneration. The average duration of all cases was $21\frac{1}{2}$ days. Omitting three cases in which the duration was 53, 136, and 42 days respectively, and in all of which the interstitial lesions were slight, the average duration of the 40 cases was 16 days. The age varied curiously with the degree of the lesions. In 19 cases in which the lesions were of slight extent the average age was two and one-sixth years; in 11 cases of medium intensity seven and one-half years; and in the remaining cases, in which lesions were extensive, eleven and one-half years. There was some relation between the lesions and the degree and duration of the affection; the lighter cases were of shorter duration, but this relation was not so marked as was the relation between the age and intensity. This shows that the interstitial process takes some time for its development and the younger cases do not live sufficiently long for the process to reach its maximum. There are some striking exceptions to this statement; in the two most extensive cases the ages were two and two and one-half years. Complications with other diseases play a more important role than in the degenerations. Scarlet fever was found in 13 cases, measles in 5, being three times more common than in the degenerations. Various other complications, such as bronchopneumonia, otitis media, etc., were but slightly more common than in the degenerations. Tuberculosis was present in 10 of the 43 cases of interstitial nephritis, and in 15 of the 112 cases of degeneration. General infection with diphtheria bacilli or streptococci was slightly more frequent than in the degenerations, and they were frequently found in the cultures from the kidney. In 15 cases the urine was tested for albumen, and in 1 case the sediment was examined microscopically. Albumen was present in 14 cases. In the one case in which the sediment was examined numerous leucocytes were found in it. In this case the interstitial infiltration was most extensive, and it is possible that the cells found in the urine may have been of the same character as those in the interstitial tissue.

3. *Glomerular changes.* — Glomerulo-nephritis was found in 11 cases. We have considered under this head all those cases in which lesions in the glomeruli were so marked as to constitute the most important lesions in the tissue. Lesions in the glomeruli play but little part in the cases of simple degeneration or of acute interstitial changes. In most of the cases of degeneration it was not possible to make out the condition of the epithelium covering the vascular tufts. In one case the epithelium of the capsule was swollen and filled with hyalin for a short distance adjoining the exit of the tubule, and an occasional swollen capsular cell was found attached to the tufts. There was usually a small amount of granular material, evidently coagulated albumen, in the capsular space. The glomeruli took no part in the acute interstitial cases. The interstitial infiltration was usually prominent around the glomerulus, but there were no cell accumulations between the capillaries or in the capsular space. Even in those cases in which the vessels elsewhere in the kidney contained large numbers of cells, the vessels of the glomeruli were generally entirely free or contained but a few scattered ones. In a number of cases large marrow cells similar to those so frequently found in the capillaries of the lung were found in the vessels of the glomeruli. In one case in which acute interstitial lesions were found along with well marked glomerular lesions a few of the cells in the glomerular vessels were similar to those in the interstitial tissue.

The changes in the glomeruli were more easily studied in the kidneys of children than of adults, owing to the greater simplicity of the glomerular structure. Important assistance was rendered by the connective stain of Mallory, which enabled us to distinguish the walls of the vessels much more clearly than by any other method. The walls of the vessels composing the glomerulus are thicker and more homogeneous than vessels of a similar size elsewhere; they stain a bright blue color and resemble the membrana propria around the tubules.

In nine of the cases the changes in the glomeruli were of the same general character, varying only in intensity and chron-

icity. From the study of the glomeruli in these cases, and of the different glomeruli in the same case, it was possible to obtain a fair idea of the character and progress of the lesions. In most cases there was very little difference in the degree of involvement of the different glomeruli in the same kidney. The first evidence of change in the glomeruli is an increase in the number of cells. (Plate XXVI., Figs. 1 and 2.) Some of the cells in the capillaries appear to be free, but others are apparently seated on the wall and project into the lumina. Red blood corpuscles may be found within the vessels, and the changes may be so slight as easily to be overlooked. From this condition the process increases in intensity by continued formation of cells. The glomerulus becomes converted into a confused mass in which it is difficult to distinguish the single capillaries. (Plate XXVI., Fig. 3.) These become entirely occluded by the increased cell formation and thickening of the wall. All the vessels of the glomerulus may be affected, but in most cases single dilated vessels containing red blood corpuscles may be found. At this period the lobulation of the glomerulus begins to be very evident and some of the lobules are converted into homogeneous hyaline masses containing numerous small irregular nuclei. In the hyaline mass the vessels may be represented by small, irregular, empty spaces. In a further degree of the process they may be entirely occluded, and the entire glomerulus represented by a hyaline lobulated mass. There is usually some enlargement of the entire glomerulus, and small masses of it may project for some distance into the tubule passing from it. The occlusion of the vessels and the formation of hyalin is produced both by hyaline thickening of the wall and hyaline degeneration of the cells. The character of the cells within the capillaries can be made out only in the least advanced cases. In cases uncomplicated by necrosis the cells were almost entirely of an epithelioid type and were derived by proliferation of the vascular endothelium, as was shown by the presence of nuclear figures. (Plate XXVI., Fig. 2.) Polynuclear leucocytes were very rare and an occasional lymphoid cell was found. With these changes in the vas-

cular type there was a varying degree of involvement of the covering epithelium. In some of the cases this was not evident at all. In others the epithelial cells were enlarged, increased in number, and covered some of the lobules as a cap; occasionally a large number of these cells was found in the capsular space. We have never found it possible to make two types of these glomerular lesions. The vascular changes may be accompanied by a varying degree of proliferation of the covering epithelium, but the latter is not found alone. In two cases the lesions had a different character. One of these was complicated by erysipelas and in the other the diphtheria was secondary to epidemic cerebro-spinal meningitis. In these two cases, particularly in the latter, there was extensive necrosis of the glomeruli with hæmorrhage into the capsular spaces. In the case secondary to the meningitis the glomeruli were in many cases surrounded by masses of hyaline material in which both fibrin and red blood corpuscles were included. (Plate XXVI., Fig. 5.) This hyaline material passed for a considerable distance into the tubule which led from the glomerulus, and the entire proximal tubule was in some cases filled with fibrin. In the necrotic tissue of the glomerulus there were numerous polynuclear leucocytes.

The average age in the cases of glomerulo-nephritis, excluding an adult of forty-five, was greater than in either the degenerative or interstitial cases. The average duration of the disease was also greater. That this affection can take place at an early age is shown by one case of one and one-half years. The shortest duration of the disease was four days in two cases. In one of these the diphtheria was secondary to cerebro-spinal meningitis and the acute character of the changes in the glomeruli corresponded perfectly with this history. The other was in an adult of forty-five years. The glomerular lesions were of a chronic type and were probably to be referred to an acute antecedent attack of endocarditis. Four of the cases were complicated with scarlet fever, one with measles, and one with both scarlet fever and measles. In two of the cases there was a general

infection with the diphtheria bacillus, in four general infection with the streptococcus. In cultures from the kidney the diphtheria bacillus was found in two cases, the streptococcus in four, the staphylococcus aureus in one, and the pneumococcus in one.

4. *Hæmorrhage*. — Slight hæmorrhages were found in the kidneys in three cases, but the hæmorrhagic type of nephritis in but one. In this case the tubules over large areas as well as the interstitial tissue contained great numbers of red blood corpuscles. No hæmorrhage was found in the glomeruli. The case was a child two years old who died on the third day from severe uncomplicated diphtheria. In the other cases which were of the glomerular type, in one, blood corpuscles were found in the capsular space and in the proximal tubules. In the other the blood evidently came from interstitial hæmorrhages in the pyramids. In the cortex occasionally entire series of distal convoluted tubules were filled with blood which had either backed up into them from the collecting tubules or had come from the ascending branch of Henle's loop. The hæmorrhage rendered it easily possible to follow the tubules in serial sections, and in one instance the hæmorrhage was traced into the collecting tubule; the loops of Henle were free. We have been much surprised at the rarity of hæmorrhages in these cases. Almost all the writers on the lesions in the kidneys in diphtheria refer to hæmorrhages, and by some they have been regarded as the chief lesion. Cases of hæmorrhagic nephritis in diphtheria have also been described clinically, although Baginsky calls attention to the infrequency of red blood corpuscles in the urine.

5. *Chronic changes*. — There were four cases in which there were well marked chronic lesions consisting of atrophy of tubules and increase in connective tissue. In two in which the duration of the disease in one was three and in the other two days, the interstitial change was well marked and evidently had nothing to do with the diphtheria. In one case, a child one year old, dying on the third day of the disease, there was a circumscribed focus of atrophy with connective

tissue formation just beneath the capsule, a condition which certainly should be referred to some antecedent condition. In the other case, a child two and a half years of age, dying on the twentieth day of the disease, there was slight acute degeneration of the epithelium and numerous small foci of cellular infiltration, increase in connective tissue, and atrophy. In these foci there was almost invariably an atrophied glomerulus and the focus probably represented the area of tubules belonging to it, but this relation could not be made out with certainty, nor could it be determined whether the lesion belonged to the diphtheria or antedated it.

No bacteria were found in the kidneys on microscopic examination.

Summary.

Lesions of the kidney varying from simple degeneration to the more serious conditions of acute nephritis are found in all fatal cases of diphtheria. Some of the lesions are somewhat more common in the mixed infections of diphtheria combined with scarlet fever than in pure diphtheria. The more severe forms of degeneration are found in those cases of diphtheria of great intensity which die shortly after the onset. The interstitial and glomerular lesions are more common in older children and in cases of longer duration of the disease, though these conditions usually are combined. There is no type of lesion peculiar to diphtheria. The lesions in the kidneys are not due to the presence of bacteria in the blood, but to the action of injurious substances in solution in the blood.

LYMPH NODES.

Lesions in the lymph nodes must be considered as among the most constant changes produced in diphtheria. The character of these lesions was first studied by Bizzozero. He described the necroses in the lymph nodules of the spleen and found very similar changes in the lymph nodes. The swelling of the nodes he attributed to an increase in the lymphoid cells. Oertel devotes a great deal of attention to the changes in the lymph nodes. He found the most marked

changes in those lymph nodes which were contiguous to the seat of primary lesion. The cervical and sub-maxillary nodes were swollen and there were small hæmorrhages in the connective tissue capsule. Sections showed an intense infiltration with cells, so that the distinction between the lymphoid tissue and the sinuses was obscured. With a low power small pale foci were observed chiefly in the peripheral nodules. These foci were formed of degenerated cells which were often included in large cells. He found in the nodes a large number of cells of various sorts, many of them much larger than the lymphoid cells, and some processes of direct and indirect cell division were observed. He gives a very good description of the character of the nuclear detritus which results from the necrosis of the lymphoid cells. He found similar changes, though less marked, in the more remote lymph nodes. Bullock and Schmorl found only inflammatory changes in the nodes in the lighter cases of diphtheria. In the more severe cases the nodes were enlarged and of firm consistency. In the peri-nodular tissue there was hæmorrhage, and yellowish streaks were frequently seen which represented lymphatics filled with fibrin. In the least altered nodes there was simply cell hyperplasia which might be so considerable that the sinuses could not be distinguished from the lymphoid tissue. In the more severe cases the necrotic foci described by Oertel were found in the lymph nodules. These writers described particularly the formation of fibrin in connection with the necrosis. In the later stages, according to them, the fibrin may disappear or be converted into hyalin. The perinodular hæmorrhages were most marked in the cervical nodes of children on whom tracheotomy had been performed. The cervical nodes were most affected, the bronchial only when there was bronchitis. They found bacilli in the nodes in 11 out of 14 cases and think the lesions may be due to their presence. The most recent work of Barbacci adds but little. He found nuclear fragmentation in the lymph nodules and numerous karyokinetic figures indicating cell division. In the remainder of the tissue there was œdema, hyperæmia, and frequently hæmorrhage. The vas-

cular endothelium was swollen and many of the cells desquamated. The vessels were often plugged with fibrin, and fibrin was found in the sinuses and parenchyma. The experimental lesions in the lymph nodes have been most carefully described by Flexner. He finds lesions both in the nuclei and in the protoplasm of the cells, which may be diffuse, affecting all parts of the node, or occur in definite foci. These lesions are seen both in lymphoid cells and in large swollen cells, phagocytic in character, great numbers of which are found in the nodes. Most of the changes in the nuclei precede degeneration, but proliferation takes place actively, both by direct and indirect division. The degenerative changes are more marked in the cortex of the node. Nearly all of the nuclear detritus is contained in cells which may be of colossal size. He thinks the large phagocytic cells are probably derived from the cells of the germinal centres. Bezancon and Labbe compare the action of the diphtheria bacilli on the lymph nodes with that produced by the injection of the toxin. They find an active inflammation produced in the adjacent nodes by the injection of the bacilli. There is no necrosis, but an abundant infiltration of the tissue with polynuclear leucocytes. Bacilli are found in the interior of phagocytic cells shortly before the death of the animal. After the injection of the toxins the inflammatory reaction is absent and early necrosis of the cells takes place.

The nodes most affected are those connected with the seat of the primary lesions, the tonsils, and the cervical nodes. Next in the frequency and extent of the lesions are the bronchial, the intestinal, and the mesenteric nodes. The distant lymph nodes, such as the inguinal and axillary nodes, are but slightly if at all affected. Macroscopically the affected nodes are enlarged, soft, and hyperæmic; in some cases there is extensive hæmorrhage in and around the node, and in rare cases suppuration occurs.

The lymph nodes were examined in 109 cases; this number includes cases of all ages and duration of disease.

Usually the examination was confined to those nodes which were manifestly affected, though in a few cases all the principal nodes of the body were examined. The tissue was hardened in Zenker, cut in paraffin, and stained with hæmatoxylin, methylene blue and eosin, and Mallory's connective tissue stain. The latter stain was most serviceable in demonstrating the reticulum of the tissue.

The most common condition found on microscopic examination was a sharp separation between the lymphoid tissue and the sinuses, due to dilatation of the latter. (Plate XX., Fig. 1.) The enlargement of the node was not due to hyperplasia of the lymphoid cells, though there was some evidence of this in most cases. The lymph nodules themselves were little if at all enlarged, and when they were enlarged this was due chiefly to the separation of the cells by œdema. The dilatation of the sinuses was more marked in the peripheral sinus than elsewhere. (Plate XX., Fig. 4.) The dilated sinuses were in some cases closely packed with cells; in others they contained but few cells and a variable amount of granular coagulum. The cells in the sinuses varied greatly in character. Polynuclear leucocytes were present to some degree in all cases and in some the sinuses were packed with them. This was particularly the case in one of the bronchial nodes examined. The leucocytes were in most cases well preserved; in others there was degeneration with the formation of nuclear detritus. A variable number of lymphoid cells were present, and in one case the sinuses contained almost as many as the lymph nodules. Even in this instance there was not much hyperplasia; there was, however, a general œdema of the tissue, and the enclosing reticulum of the lymphoid tissue was dilated, giving free entrance to the cells of the lymphoid tissue into the sinuses. The separation between the lymphoid tissue and the sinuses was very evident, particularly in the specimens stained with the connective tissue stain. It shows a reticulum throughout the node, which is connected with the capsule. The sinuses are crossed by fibres of reticulum which are connected with the fine reticulum of the lymphoid tissue. Each lymph nodule is sur-

rounded by a condensation of reticulum which forms an imperfect capsule around it in which there are numerous spaces connecting the interior of the nodule with the sinus. The reticulum of the nodule is more abundant in the periphery; in the centre it may be entirely absent. The separation of the spaces in the reticulum by œdema will render it much more easy for the cells of the nodules to pass into the sinuses.

In addition to the lymphoid cells and polynuclear leucocytes it is possible to distinguish three other varieties of cells in the sinuses. The most striking of these are cells of apparently the same character as the mononuclear leucocytes. (Page 225, and foot-note.) They were present in all cases and in some were so abundant that the dilated sinuses were crowded with them. They were either diffusely scattered in the sinuses or collected into masses. The same description of them which has been given in the lungs and elsewhere applies here. They are of the same size or a little larger than the polynuclear leucocytes. The protoplasm stains sharply with eosin and contains no distinct granules. The periphery is more irregular than that of the polynuclear leucocyte, and the definite membrane of the latter is absent. The nucleus is vesicular and may be round, oval, or almost as much curved as the nucleus of the polynuclear leucocyte. No transitions were seen between these cells and the polynuclear leucocytes, nor was there any relation between them in the respective numbers present. These cells were apparently formed in the lymph node. The efferent lymphatics often contained considerable numbers of them, and in the few cases in which the afferent lymphatics could be made out they were not present in these. Certainly no transitions could be seen between these and the lymphoid cells. In some of the cases of general œdema of the node a few non-granular cells were found within the lymph nodules, but they were not generally present. It seems to us most probable that they are derived from proliferation of the endothelial cells lining the sinuses. In one case particularly, in which there was great dilatation of the sinuses, there was evident

proliferation of the endothelium of the sinus and nuclear figures were found in the cells. In a normal node it is difficult to demonstrate this endothelium which lines the sinus and invests the intersecting fibres, but it was perfectly evident in the œdematous nodes. In the case referred to, groups of two or three nuclei were found in the endothelium, and in a few places cells of the same character as those contained in the sinuses adhered to the fibres. We could not make out the relation of these endothelial cells within the lymph nodules to the reticulum; there was only an occasional nucleus here of the same character as those lining the sinus. Another possible source of these cells is from proliferation of the endothelium of the small blood vessels. This was most marked in some cases both in the vessels in the sinuses and in the thin-walled vessels of the lymph nodules. The nuclei are large, project into the lumen, and often have their long axes perpendicular to the axis of the vessel. Cross-sections of these small veins often resemble glands. In one instance several of these cells were found overlying one another and almost occluding the small vein. Cells similar to those within the vessel were found on the outside.

Cells distinguished by their phagocytic properties were also numerous in the sinuses. These cells presented considerable variation in size, but all seemed to be of the same character. Some were not larger than the cells they enclosed; others were very large and enclosed as many as twelve other cells. Their outlines were irregular, the protoplasm indistinctly granular. The nucleus was large, generally oval, and vesicular. It always stained less distinctly than the nuclei of the enclosed cells and in some cases was difficult to distinguish. The cells enclosed in the phagocytic cells always lay in vacuoles. In rare cases two or more cells were enclosed in the same vacuole. The enclosed cells were in some cases well preserved, so that their character could be distinguished; in others they had undergone degeneration, and the nuclei had given rise to nuclear detritus. The principal cells enclosed in the phagocytic cells were either lymphoid or plasma cells. Polynuclear leucocytes were occa-

sionally found in them. The most common cell found in the sinuses, the nongranular cell, or endothelial cell, was never found enclosed in the phagocytic cells. It seems to us that the phagocytic cells are of the same character as the nongranular cells. Every transition can be seen between the large phagocytic cells and cells which are evidently nongranular leucocytes. Both nucleus and protoplasm have the same characteristics of staining as the nongranular cells. Phagocytic cells occasionally were found attached to the reticulum within the sinus.

The sinuses also contained a variable number of large cells having some similarity to the cells of the germ centres of the lymph nodules, but very much larger than these. They are found both in the sinuses and in the nodules, and in some cases are in such number as to form the principal cell in the node. They vary in size and are often double or three times the size of a red blood corpuscle. The outline is irregular and the protoplasm granular. The granules are not regularly round, vary greatly in size, are often apparently joined in small clumps; they stain brightly with methylene blue. The granules appear to be loosely enclosed in the cytoplasm; they project from the edge of the cell, and numbers of granules of the same character as those enclosed in the cells may be found free in the vicinity. We were not able to make out whether these were extruded from the cells or whether they were due to breaking up of the cell protoplasm in the manipulation of cutting, etc. The nucleus is relatively large for the size of the cell, stains very brightly, and is somewhat vesicular in character. The chromatin is arranged in granules around the periphery of the nucleus and in two or three large masses in the centre which are connected by chromatin filaments. Nuclear figures are often found in these cells. When they are present the cell protoplasm is more granular; the granules are larger and stain more brightly. These cells more nearly approach the lymphoid cells in some of their characteristics than any others, and from their presence in both the lymph nodules and sinuses they seem to be derived from these. On division they

give rise to cells of a similar character. These cells are perfectly distinct from the plasma cells, numbers of which are often present both in the sinuses and in the lymphoid tissue. In lymph nodes which are much affected they are often found in the capsule and in the surrounding tissue.

A few eosinophile cells are always found, and in some cases considerable numbers of them. There are two distinct forms of these, one with a nucleus very similar to that of the polynuclear leucocyte, and the other with a nucleus similar to that of the plasma cell. The latter were found in one case in considerable numbers among the plasma cells in the capsule of the node, and seemed to be formed from these. In some of these cells there was an accumulation of eosinophile granules around or on one side of the nucleus, the remainder of the protoplasm being unchanged. In other cases the granules filled the entire cell.

In nearly all the nodes there was congestion and the blood vessels were evident. In several there was hæmorrhage involving a part of or the entire node. The hæmorrhage often extended into the surrounding tissue. In the slightest cases only a few red corpuscles were found in the sinuses among the other cells, and in the most marked cases both sinuses and nodules were packed with them. In the extreme cases there was a general necrosis of the tissue combined with the hæmorrhage. These extensive hæmorrhages were, almost without exception, found in cases of great severity in which death took place early in the disease. The longest duration was eleven days, and the average of ten cases was four days. The cervical nodes were almost the only ones so affected. There was no especial feature in the bacteriology of these cases.

In addition to the extensive necrosis of tissue combined with hæmorrhage, more or less circumscribed necrosis, combined with leucocytic infiltration, was found in a number of cases. This necrosis did not differ from necrosis found in other situations (Plate XIX., Fig 4) The necrotic area contained comparatively little nuclear detritus except that which was derived from the infiltrating polynuclear leucocytes.

These foci were exclusively found in the periphery of the node adjoining the peripheral sinus. In one case great numbers of streptococci were found in the necrotic tissue, and in one case staphylococci. In but three cases of the entire number was there a definite suppuration. In a number of cases there was a diffuse necrosis extending throughout the entire node, and affecting scattered cells both in the lymph nodules and in the sinuses. It was more marked in the periphery of the node than in the centre, and was shown by scattered nuclear fragments. In no case was it very extensive.

Fibrin was found in variable amount in connection with the hæmorrhages and circumscribed necroses. In several cases the dilated sinuses contained a great deal of fibrin.

The lesions of the nodes which have been described have nothing characteristic about them. They may be found in the nodes in a great number of pathological processes. The most interesting and in some respects the most characteristic lesion of the disease, and the one which was found in the greatest number of cases, consisted in the formation of discrete foci due to cell proliferation combined with necrosis. (Plate XIX., Fig. 3; Plate XX., Fig. 1.) These foci generally have been considered as formed by a simple necrosis of the tissue due to the action of toxic substances. In the large number of cases at our disposal every stage of the process could be followed; we were also aided by the very thin sections which were cut on the Blake-Minot microtome. These foci were formed exclusively in the lymph nodules and were more numerous and larger in the periphery of the node than in the centre. We shall give the structure and mode of formation of these foci, as we have learned it from the study of a great number of cases, and omit the description of single cases. The first step consists in the appearance of a group of cells among the lymphoid cells. These cells have a faintly stained vesicular nucleus and a large amount of pale, faintly granular protoplasm which stains with eosin. The cell outlines are faint and irregular. The cells usually are fused together into a mass in which the pale vesicular nuclei

are embedded. (Plate XX., Fig. 2.) Single cells of this sort are occasionally found in the periphery not joined with the main mass. (Plate XX., Fig. 3.) Even when the cells are joined in a mass, round spaces are occasionally found, giving to it a more or less reticular structure. At this stage there is often a striking similarity to the structure of a small miliary tubercle without giant cells. The size varies greatly, but generally is about that of a small miliary tubercle. With a low power the foci are very evident, standing out sharply from the surrounding lymphoid tissue. They are rendered much more evident by the close packing of the lymphoid cells around them. The smallest and apparently the youngest foci are often formed of these large cells alone. In other cases a variable number of lymphoid cells are found among them. The large cells are phagocytic, and in the larger nodules almost invariably contain enclosed within them lymphoid cells which show every stage of nuclear degeneration. In some cases the lymphoid cells are enclosed in definite vacuoles in the larger cells, but in most cases they are so degenerated that only the fragments of the nuclei are found. The nuclear detritus coming from the lymphoid cells is different from that derived from other cells, particularly from polynuclear leucocytes. The first stage in the degeneration is shown in the accumulation of chromatin in a thick mass around the periphery of the nucleus. Sometimes it forms a regular circle, or it may accumulate at two or three points. It then divides sometimes into two masses or into a number of small fragments which in nearly all cases are distinctly round and show a darkly stained periphery and a clear centre. In some cases the dark stained masses are distinctly crescentic in form. Even when the nucleus breaks up into exceedingly small fragments not larger than cocci this same peculiarity of staining is found. The nuclear detritus derived from other cells is always more irregular in form. The number of cells included in the large phagocytic cells and the amount of nuclear detritus varies greatly. It is always more abundant at the periphery of the nodule, which is often surrounded by a dark line formed of nuclear detritus. The degeneration

often extends beyond the foci, so that a number of large cells are nearly always found among the lymphoid cells and the same process of phagocytosis takes place in them. It is only in very young foci that the process, as we have described it, can be followed. It becomes complicated by the degeneration which the entire focus, including the phagocytic cells, undergoes. These cells lose their distinctness, the nucleus swells, becomes more vesicular, appearing only as a faint outline, and finally degenerates and itself gives rise to nuclear detritus. At this stage we can recognize in the focus a more or less irregular central area in which there is considerable nuclear detritus, and this is surrounded by a dense zone of nuclear detritus. This formation of discrete foci may be the only change in the node or it may be combined with the various processes described. There may be a greater or less amount of diffuse necrosis in the surrounding lymphoid tissue, but this is totally different from the phagocytosis with degeneration which takes place in the nodule. The process may be further complicated by hæmorrhage and fibrin formation. Hæmorrhage into a focus may take place at the beginning of its formation, and red blood corpuscles may be found among the other cells or enclosed in the phagocytes. Fibrin formation may accompany the hæmorrhage, but is more frequently seen without it. The fibrin may be limited to small areas or the whole focus may be filled with it. It is always more abundant in the periphery than in the centre. From the combination of hæmorrhage and fibrin formation the entire focus may be converted into a hard compact mass which is more resistant to disintegrating processes than the surrounding tissue. This was very evident in the tonsils in the cases in which ulceration and softening extended into the lymphoid tissue from the crypts; the foci formed round masses lying loosely in the tissue. Polynuclear leucocytes take little or no part in the formation of these foci. They are but rarely found among the other cells. Even when there is extensive necrosis the necrotic tissue seems to exert but little attraction for them.

We have already alluded to the resemblance between these

foci and tubercles; the foci, like the tubercles, contain no vessels. We are unable to state with certainty how the large cells are formed. They are certainly not formed from any variety of the lymphoid cells or from polynuclear leucocytes. The only cells in the lymph nodules from which they could arise would seem to us to be the cells covering the reticulum. It is, however, possible that the cells lining the lymphatics or even the capillary cells may take some part in the formation. In several cases there was evident proliferation of the cells of the vessels, and in one case a focus seemed to be formed around a vessel. The occlusion of the vessels was probably due to proliferation of the endothelium with subsequent degeneration of the cells. There is no continuous formation of large cells. Nuclear figures were searched for in them, but never found. In some cases there seemed to be direct division of the nuclei, but this did not lead to the formation of new cells.

Tonsils.

The lesions in the lymphoid tissue of the tonsils differ somewhat from the lesions in the other lymphoid tissue. They are constantly found and in most cases are much more marked.

The lymphoid tissue of the tonsils differs from that of the lymph nodes in the large size of the lymph nodules and the great development of the so-called germ centres in them. These are circumscribed masses of cells which differ considerably in character from the lymphoid cells around them. The nucleus is larger than that of the lymphoid cells, often double the size; it is paler and contains fewer granules. It is usually round or oval in outline and may be slightly curved. The protoplasm is more abundant than in the lymphoid cells, ragged in outline, and stains with methylene blue. The cells have much similarity to the large cells of lymphoid character which we have described in the sinuses and lymph nodules of the lymph nodes. Nuclear figures are very abundant in them, and the name "germ centre" has been given to them by Fleming from the supposition that the new

formation of lymphoid cells takes place chiefly or exclusively from these cells. These germ centres do not form a constant constituent of the lymph node. They are invariably present in the tonsils and in the lymph nodes of the intestinal canal in children. They may be found in the bronchial lymph nodes and are generally absent elsewhere. They are always larger and more numerous in children than in adults. We have never been able to satisfy ourselves that the new formation of lymphoid cells takes place exclusively from proliferation of the cells composing the germ centres, or that there is a constant relation between the presence of germ centres and proliferation of lymphoid cells. In the tonsils the lymphoid cells are closely packed around the germ centres, especially on the side nearest the crypts, where the compact mass of cells has a crescentic shape. In all the tonsils examined there was never the sharp separation between the lymph sinuses and the lymph nodules which was so often seen in the other lymphoid tissue, and usually the lymph nodules could be recognized only by the pale germ centres. Generally the tissue was formed of a mass of cells, principally small lymphoid cells, a variable number of plasma cells, and large lymphoid cells. We very rarely found the large mononuclear leucocytes with oval nuclei which were so abundant in the sinuses of the lymph nodes. The lymphoid and plasma cells were not confined to the tissue of the tonsil, but often extended as a diffuse infiltration far into the surrounding tissue. Phagocytic cells were occasionally seen, but they were never so abundant as in the sinuses of the nodes. The foci composed of phagocytic epithelioid cells were found both among the lymphoid cells and in the germ centres. Both a diffuse necrosis affecting single cells and necrosis and ulceration extending into the tonsils from the crypt were frequently found. In several cases there had been membrane formation secondary to the ulceration, and a fibrinous membrane formed directly in the lymphoid tissue; in these cases the reticulum was apparently converted into hyaline fibrin. In a number of cases there was extensive hæmorrhage accompanied by fibrin and necrosis. Fibrinous exudation without hæmor-

rhage was also frequently found. Micro-organisms were rarely found in the tissue on microscopic examination; the most frequent organism was the streptococcus, which was found in four cases.

Summary.

The lymph nodes are affected in nearly all cases of diphtheria. The lesions are most marked in the nodes which are nearest to the primary lesions and rarely extend to the distant nodes. The lesions are most marked in cases of great intensity in which death takes place early. Two sorts of lesions may be recognized:

1st. The ordinary lesions which may follow an injury of almost any sort and which consist in congestion, hæmorrhage, and diffuse and circumscribed necrosis. Numerous cells, not ordinarily found in the tissue, appear in combination with these processes. These new cells are derived in part from the lymphoid cells and in part from proliferation of the endothelial cells of the sinuses and reticulum. There is little or no increase in the number of lymphoid cells. The swelling of the nodes is due chiefly to congestion, hæmorrhage, and dilatation of the sinuses.

2d. Lesions which are distinctive of diphtheria, but which may be found in other infectious diseases of children. These lesions consist of the formation of foci which are very similar in appearance to miliary tubercles. In the formation of these foci there is a combination of proliferation, phagocytosis, and degeneration. Proliferation, most probably of the endothelial cells of the reticulum and possibly of the vessels, gives rise to the formation of large cells resembling the epithelioid cells of the tubercle. These cells devour the lymphoid cells and from these the nuclear detritus is chiefly derived. Afterwards the large cells themselves undergo necrosis and their nuclei give rise to nuclear detritus. Caseation is never produced, nor are giant cells formed in connection with the nodules. In all these changes in the lymph nodes bacteria play but little part directly. We have never found the diphtheria bacilli in the nodes and only rarely the pyo-

genic cocci; the latter are always in combination with necrosis and hæmorrhage. The lesions are due to the absorption of the toxic products of the diphtheria bacilli and other organisms. These toxic products are brought to the node by the lymphatics, and all the lesions are most pronounced in the vicinity of the afferent lymphatics.

THYMUS.

We have not been able to find any references to the examination of the human thymus in diphtheria. In his study of experimental lesions Flexner found the same lesions in the thymus as in the lymphatic tissue elsewhere. He calls attention to the frequency with which the degenerated cells were found in the neighborhood of the Hassel bodies.

We have examined the thymus in 20 cases, the ages extending from seven months to five years, and the duration of the disease from two to sixteen days; most of them were under six days. For the sake of comparison we have examined the thymus of a child ten days old which died of inanition, and of a child ten months old which died of dysentery. The thymus of the latter showed conditions very similar to those which we have found in diphtheria. There was a very marked difference in the size of the glands in the different cases, and this was not dependent on the age. A small and atrophic gland was found in a child fifteen months old and a large well-developed gland in a child of five years. The thymus has some resemblance in its structure to the lymph node. It is composed chiefly of lymphoid cells which lie in large masses separated by bands of loose connective tissue containing numerous cells. There is no division of the lymphoid tissue into lymph nodules and sinuses. There are numerous blood and lymphatic vessels which are contained both in the lymphoid tissue and in the connective tissue septa. The lymphoid cells are of both the small and the large variety, and among them there are numerous large cells with vesicular nuclei. No so-called germ centres were found in the lymphoid tissue. Lying generally in the middle of the lymphoid tissue are large cells

of a distinctly pavement epithelial type frequently arranged in concentric masses. They stain intensely with eosin and the nuclei are faint and indistinct. There are numerous eosinophile cells in their vicinity. In the thymus of the child of ten days no degenerative conditions were found in the tissue; in that of the ten-months' child degenerated lymphoid cells were found in the large cells and there was some diffuse degeneration.

The principal change found in the diphtheria cases was degeneration of the lymphoid cells. The nuclei showed the peculiar forms of detritus seen in these cells. The degeneration was most marked in the vicinity of the Hassel bodies, and the degenerated cells were most frequently included in the large cells with vesicular nuclei. The degeneration was much more diffuse than in the lymph nodes, and the definite nodules of epithelioid and degenerated lymphoid cells were not found. In addition to this there was diffuse degeneration of the lymphoid cells forming small masses of nuclear detritus scattered through the tissue. Brightly staining eosinophile cells were very numerous in all cases, and more numerous than in the cases used for comparison. They were single and scattered through the tissue, or in masses chiefly in the vicinity of the Hassel bodies. The eosinophile cells are large and uninuclear. Nuclear figures were frequently found in them. The eosinophile cells were never included in other cells, nor did they contain inclusions. Very few polynuclear leucocytes were found in the tissue. A few eosinophile granules were also found in large cells apparently belonging to the connective tissue which were found in the connective tissue septa. The lymphatics were frequently dilated and in one case they contained great numbers of cells similar to those found in the sinuses of the lymph nodes. Hyaline degeneration of the walls of the vessels was found, and in one case, a child seven months old, who died on the seventh day of the disease, thrombi composed of polynuclear leucocytes, lymphoid cells, and a small amount of fibrin were found in a number of the small veins. No bacteria were found in the sections from any of the cases.

NERVOUS SYSTEM.

The study of the lesions of the nervous system in our cases of diphtheria has been made by Drs. J. J. Thomas and H. S. Steensland. The work on the ganglion cells has not yet been completed, that on the nerves has already for the most part been published, so that only a summary of the results obtained is included here.

In all 28 cases were examined; they were selected either on account of cardiac symptoms, paralyses, or severity of the disease. Various nerves were examined by Marchi's method: the olfactory once; the optic chiasm twice; the third cranial nerve once; the fourth twice; the fifth twice; the sixth, seventh, eighth, and ninth each once; the pneumogastric 28 times; the twelfth nerve twice; the phrenic twice; the splanchnic once; the ulnar once; the obturator once; the anterior crural three times; the sciatic twice. In addition Marchi's method was used for the cortex cerebri five times, the cerebellum twice, the pons three times, the medulla four times, the spinal cord seven times, the Gasserian ganglion once. In many cases the nerves from both sides of the body were examined, but no differences in the results obtained were observed.

All of the nerves in the 28 cases showed various degrees of fatty degeneration, from slight to extreme. The degeneration seems almost invariably to begin in the myelin sheath. Clearly to demonstrate this it is necessary to stain the axis cylinders in the Marchi preparations by means of a rather strong mixture of acid fuchsin and picric acid. In sections stained in this way the axis cylinders often are found pushed to one side, so that the drops of fat lying in the middle of the nerve fibre and apparently within the axis cylinder are clearly shown to have originated in the myelin sheath.

As a rule the change in the myelin which causes it to stain with osmic acid in the Marchi method begins at some point close to the axis cylinder and gradually spreads around and along it. The myelin breaks up into granules, droplets, and very irregular bizarre figures of which the peripheries

usually are more refractive than the centres and often doubly contoured. As a rule the centres of the masses stain more deeply than the peripheries, but sometimes small black globules appear with pale centres.

The change in the axis cylinder seems to consist chiefly of swelling which is often irregular, so that the axis cylinder presents a beaded appearance. As it swells it stains very faintly, so that it is often difficult and sometimes impossible to make it out. When the myelin sheaths have undergone marked fatty degeneration, the axis cylinders usually cannot be distinguished. Whether they have simply swelled up and disappeared, or have undergone fatty degeneration, is difficult to determine; but in no axis cylinder which could be positively demonstrated was there any evidence of fatty degeneration.

Examination of the cerebrum five times, cerebellum twice, pons three times, medulla four times, and cord seven times, showed everywhere a slight to marked diffuse fatty degeneration of the white substance. The same change was present in the anterior and posterior nerve roots.

The results of the investigation of the nervous system may be summed up as follows: There occurs in certain cases of diphtheria a slight to marked diffuse fatty degeneration of the nerve fibres of the central nervous system and of its peripheral extensions.

SKELETAL MUSCLES.

In one case in which the nerve fibres of the central nervous system and of the peripheral nerves showed marked fatty degeneration, the muscles of the tongue, of the ulnar side of the forearm, the sartorius muscle, and the biceps of the thigh were examined by Marchi's method. All showed a marked degree of fatty degeneration. About one muscle fibre in four seemed affected. The fat drops were small and usually very evenly distributed throughout the whole of the fibres affected. The heart muscle in this case also showed marked fatty degeneration. In a second case where fatty degeneration of the heart and of the nervous system was

marked, the muscles of the tongue, the diaphragm, and the tibialis anticus all showed a similar degenerative process. In places three fibres out of four were studded with fat drops. It seems probable that in all cases where fatty degeneration of the heart and of the nervous system has occurred, a similar change will be found in the skeletal muscles.

BONE MARROW.

We have been able to find but two references to the condition of the bone marrow in diphtheria, and both of these are in reference to lesions produced experimentally. Trambusti found increased granulation and proliferation of cells produced by small doses of toxin. According to him, large doses seemed to exert a paralytic action on the cells. He is inclined to think that these changes in the marrow are concerned with the production of antitoxic substances. Roger and Josue found that proliferation of the marrow cells was produced by both the toxin and antitoxin. The toxin affects the large and medium cells, the antitoxin the small. The changes produced by the toxin appear earlier than those produced by the antitoxin.

The bone marrow was examined in 48 cases. No selection was made in these cases as to the duration or character of the disease. The marrow in all cases was taken from the middle of the femur; the bone was laid bare and the upper surface chiselled off, exposing the marrow. In a few cases the tissue was hardened in formalin or in corrosive, but generally only Zenker's fluid was used. After hardening, the marrow was decalcified in 5 per cent. nitric acid for 24 hours. The sections were cut in paraffin and stained in the usual way. The marrow was perfectly preserved and the cell granules stained clearly.

In all cases the marrow was hyperplastic. (Plate XXVII., Fig. 1.) Three of the cases were in adults, the remainder in children. The hyperplasia was less marked in the adults than in the children. In the adult cases the marrow was reddish with areas of yellow fat. In the children there was

considerable difference in the character of the marrow. In most cases it was red, of firm consistency, and could be removed in solid pieces; in some cases it was more grayish and softer. Microscopic examination showed the same difference in the degree of hyperplasia. In some of the sections the marrow appeared as an almost solid cellular mass with only a few scattered fat spaces. In others the fat was more abundant, and the cell masses formed a reticular structure between the fat spaces.

It was impossible to procure normal marrow of children of different ages for comparison. The cases selected for comparison were a child ten months old which died of colitis after an illness of ten days, a child which died ten days after delivery, and a foetus of eight months. Comparison with all these cases showed a very evident hyperplasia in the diphtheria cases. In all three of the non-diphtheria cases the marrow was cellular, but neither in the abundance of cells nor in their character was there much similarity with the diphtheria cases. In one of the diphtheria cases the condition of hyperplasia was but slightly marked. This was from a child six years old which died of heart paralysis in the forty-eighth day of the disease. The marrow of this case was very similar to the marrow of the eight-months' foetus.

All of the cases presented marked differences with regard to the character and the relative numbers of the different cells in the marrow. The most prominent cells and those which were always present in large numbers were large cells which varied in size; the average size was about five times that of a lymphocyte. (Plate XXVII., Fig 2.) The nucleus was somewhat vesicular, the periphery stained sharply, and the chromatin was in granules which were in the interior of the nucleus and attached to the periphery. The chromatin granules were connected by threads. The protoplasm varied in amount, but was generally considerable relative to the nucleus; it was finely granular; the granules in some cases stained slightly with blue, in others they took a reddish tinge from the eosin. The slight eosin stain was more marked in the vicinity of the nucleus than elsewhere. These cells

were always present. They were found in small numbers in the cases selected for comparison; in the diphtheria cases the numbers of them varied, in some cases forming the great majority of all the cells present. Active proliferation of these cells was taking place and nuclear figures in great abundance were found. These cells cannot be distinguished from plasma cells, and like the plasma cells they are never phagocytic.

A variable number of lymphoid cells was always present. (Plate XXVII., Fig. 1.) In the comparison cases the lymphoid cells were relatively more abundant than in the diphtheria cases. In the diphtheria cases they were generally diffusely scattered among the other cells, but occasionally compact masses of them were found. It was never possible to show in these masses a reticulum or a similarity of structure to that of the lymph node. In one case there was a circumscribed area of necrosis in the midst of the collection of lymphoid cells. (Plate XXI., Fig. 3.) It did not extend to the adjacent marrow cells.

The number of eosinophile cells in the marrow varied greatly. They were very numerous in seven cases in which the average duration of the disease was six days. Eosinophile cells were certainly less numerous in the cases of longer duration and in the cases of greater age. There was a general agreement between longer duration and greater age in all the cases in which the marrow was examined. In the cases used for comparison there was a good deal of variation in the number of eosinophile cells, and they were most abundant in the marrow of the eight-months' foetus. The eosinophile cells presented the same variety in character and in numbers as the other cells. They were found both in groups and irregularly scattered among the other cells. In the cases in which they were most abundant areas were found almost composed of them. Many of the eosinophile cells in size and in the character of the nucleus were similar to the cells first described. Apparently transition forms between these cells which resemble plasma cells, and which should probably be considered as the most typical cells of the marrow, and eosinophiles were found. Single oxyphilic granules

appeared in the blue staining protoplasm and increased in number until they filled the cell.¹ The eosin granules varied considerably in size, and in several instances cells were found which contained large round granules similar to those found in the eosinophile cells of the horse's blood. These large eosinophile cells were in the minority. Most of them were smaller, no larger than the eosinophile cells of the blood. They usually contained a single small nucleus similar to that of the lymphoid cell; in other cases two nuclei were found, or the nucleus was curved or even as irregular as the nucleus of the polynuclear cell. In the cases in which the eosinophile cells were most abundant, numerous eosinophile granules were found scattered in the tissue. This condition is probably an artefact resulting from the breaking up of the cells in cutting the sections. Nuclear figures were found in small numbers in the eosinophile cells. They were most numerous in the larger cells.

Polynuclear leucocytes were found in very small numbers. They were never in groups, but irregularly distributed among the other cells. A few cells of a definite endothelial character similar to those described in the other tissues were found. These cells here also showed their phagocytic character, and both polynuclear leucocytes and lymphoid cells, principally the latter, were found enclosed in them.

There was considerable variation in the number of large myeloplaques in the different cases. There was considerable variety among them and it was not certain if they represented different forms of the same cell. The most abundant were large cells with finely granular protoplasm which stained slightly with methylene blue. Occasionally definite blue granules were found in the protoplasm, or one part of the cell stained more distinctly than another. There were often a number of round, oval, and vesicular nuclei in these cells. In some cases, instead of a number of separate nuclei, a large irregular nuclear mass was found, which often presented the appearance of a central mass with knob-like projections ex-

¹ Howard has recently advanced the view that in various organs eosinophilic cells are formed from plasma cells.

tending from it. The periphery of the nuclear mass often stained intensely, or large threads of chromatin resembling fibrin passed through it. Often the cell may be almost filled with an extremely irregular nucleus showing a large vesicular mass at the periphery. Another variety of these myeloplaques consists of cells somewhat smaller than these just described, with a large amount of structureless chromatin in the cell. The mass of chromatin stains homogeneously and intensely. There is still a third variety of cells which is smaller than either of the others, and which contains a solid, structureless, intensely staining nucleus.

Cells similar to those described in the marrow were found in the veins in nearly all cases. In three cases the large myeloplaques were found in the veins enclosed in a mass of red blood corpuscles, so that their presence there could not have been due to an artefact. These were evidently the cells which we have described in the capillaries of the lung and in the vessels of the glomeruli.

In nearly all cases a variable number of nucleated red corpuscles were found in the marrow. They were easily recognized by the intensely stained structureless nucleus and by the outside rim of the corpuscle.

Very little connective tissue was found in the marrow and that was along the arteries. The veins are numerous and their walls have almost a capillary structure. Red blood corpuscles were found outside the vessels among the other cells, but there was in no case any extensive hæmorrhage.

It is difficult to find what is the relation of the condition of the marrow to the other features of the disease. It is certain that all the varieties of cells in the marrow are continually entering into the blood; the way of entrance is given by the thin walls of the veins and their close relation to the marrow cells. Cells in all respects similar to those in the marrow are found in the vessels there and in the vessels in other organs. It seems probable to us that the cells found in the interstitial tissue of various organs are derived from the marrow, but this is hardly their exclusive source. It is possible that the ordinary marrow cell is the same as the plasma cell, and

that the slight differences in size and staining may be due to the decalcifying process. Our knowledge of the structure of the marrow at different ages is very incomplete. It was not possible to obtain this knowledge from our autopsies, as they were all cases of infectious disease. The condition of the marrow which we have described is not confined to diphtheria. We have found the same changes in diphtheria, scarlet fever, measles, and other infections.

PANCREAS, ADRENALS, THYROID GLAND, SALIVARY GLANDS,
TESTICLES, AND PITUITARY BODY.

These glands showed no macroscopic changes. We have examined them microscopically in a large number of cases with negative results. In one section a superficial necrosis with purulent infiltration was found in a submaxillary gland due to an extension of the infectious inflammation from the throat. It is remarkable that no lesions were found in the adrenal glands, for congestion, hæmorrhage, and foci of necrosis in these are the most common lesions in the disease produced experimentally, either when the bacilli are inoculated or the toxins injected (Welch and Flexner, and J. H. Wright).

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PLATE XV.

FIGURE 1. — Section through edge of tonsil. A dense membrane extends over a part of the surface. The large crypt in the tonsil is filled with cast-off epithelium and exudation. "a," membrane on surface denuded of epithelium. "b," adjacent unaltered mucous membrane. "c," mucous glands. "d," muscle. "e," tonsil. "f," interior of crypt.

FIGURE 2. — Section through tonsil showing crypts communicating with the surface. There are only a few shreds of membrane on the surface. On one side there is extensive fibrinous exudation within the crypts, with hæmorrhage and necrosis of the adjoining tonsillar tissue. "a," small mass of membrane on surface. "b," crypts filled with fibrinous exudation.

FIGURE 3. — Section through recently formed hyaline membrane on surface of pharynx. In the interstices of the membrane there are a few leucocytes.

FIGURE 4. — Older and denser hyaline membrane from pharynx, showing small spaces in the reticulum. Figures 3 and 4 are stained with iron hæmatoxylin.



Fig. 1

Fig. 1.

b

Fig. 2



PLATE XVI.

FIGURE 1. — Section of trachea with attached membrane. The membrane is composed of a fibrinous reticulum enclosing flattened spaces, which vary but little in size. The membrane is attached to the membrana propria by stalks of fibrin. A few of the epithelial cells of the trachea still remain beneath the membrane. The clear line beneath the membrane is the membrana propria. “a,” membrane. “b,” membrana propria.

FIGURE 2. — Section of trachea with membrane. The surface of the membrane is formed of exudation detritus and masses of bacteria; beneath this is a mass of leucocytes separated from the fibrin. Beneath the membrana propria there is extensive fibrinoid degeneration of the connective tissue. “a,” surface of membrane. “b,” layer of leucocytes. “c,” fibrin. “d,” membrana propria. “e,” fibrinoid degeneration of connective tissue.

FIGURE 3. — Section through crypt of tonsil, showing fibrinoid degeneration of tissue beneath epithelium.

FIGURE 4. — Section passing through mouth of a mucous gland of pharynx. The fibrin shows a peculiar arrangement, the fibres forming two systems of arches which are attached to the sides and to a thick mass of fibrin in the centre. Near the bottom of the space there is a small mass of epithelium.

PLATE XVII.

FIGURE 1. — Papilla of tongue covered with fibrin.

FIGURE 2. — Mucous membrane of pharynx adjoining diphtheritic membrane. The upper layers of the epidermis are in part exfoliated, in part converted into long strands, which pass upwards and are lost in the fibrin. Large numbers of leucocytes are contained in spaces in the fibrin.

FIGURE 3. — Section of the epithelium of the œsophagus, showing increase in nuclei by direct division.

FIGURE 4. — Section through mucous membrane of œsophagus adjacent to an ulcer, showing direct division and degeneration of the nuclei of the epithelium.



PLATE XVIII.

FIGURE 1. — Section through skin of ear, showing necrotic epithelium with fibrin formation.

FIGURE 2. — Diphtheria of stomach. The fibrinous exudation is attached by narrow pedicle, and spreads on either side over the surface. At "a" the epithelium is turned back and attached to the membrane. There is considerable hæmorrhage in the mucous membrane.

FIGURE 3. — Hyaline fibrinoid degeneration of the muscular coat of arteries in the mucous membrane of pharynx.

FIGURE 4. — Longitudinal section of artery, with slight hyaline formation in the muscular coat.

Fig. 1

Fig. 4.



PLATE XIX.

- FIGURE 1.** — Section of mucous membrane of pharynx, showing dilatation of superficial lymphatics.
- FIGURE 2.** — Section of mucous membrane of stomach, showing hæmorrhagic exudation between the glands near the surface.
- FIGURE 3.** — Section of lymph node containing circumscribed mass of epithelioid cells. The small dark points in the area represent nuclear detritus from lymphoid cells.
- FIGURE 4.** — Small area of necrosis in lymph node near the peripheral sinus. The necrotic tissue is invaded by polynuclear leucocytes and no epithelioid cells have been formed.



PLATE XX.

FIGURE 1. — Section of cervical lymph node, showing dilatation of the lymph sinuses, which are filled with large mononuclear cells. At "a" there is a small mass of epithelioid cells.

FIGURE 2. — Area of epithelioid cells in lymph node. "a," small vessel. "b," nuclei of epithelioid cells. "d," lymphoid cell detritus.

FIGURE 3. — Scattered epithelioid cells, some of which contain nuclear detritus. These cells lie in the œdematous tissue of the lymph nodule. There were no circumscribed areas of epithelioid tissue in the node.

FIGURE 4. — Section of œdematous lymph node, showing the peripheral lymph sinus crossed by prolongations from the capsule. "a," capsule. "b," sinus. "c," membrane separating the sinus from the lymph nodule. Section stained with the Mallory triple stain.



PLATE XXI.

FIGURE 1. — Section of myocardium, showing fatty degeneration and separation of the fibres.

FIGURE 2. — Recent blood plate thrombus in heart.

FIGURE 3. — Bone marrow, very rich in lymphoid cells, and containing a small area of necrosis and hæmorrhage.

FIGURE 4. — Myocardium, showing separation and degeneration of muscular fibres.

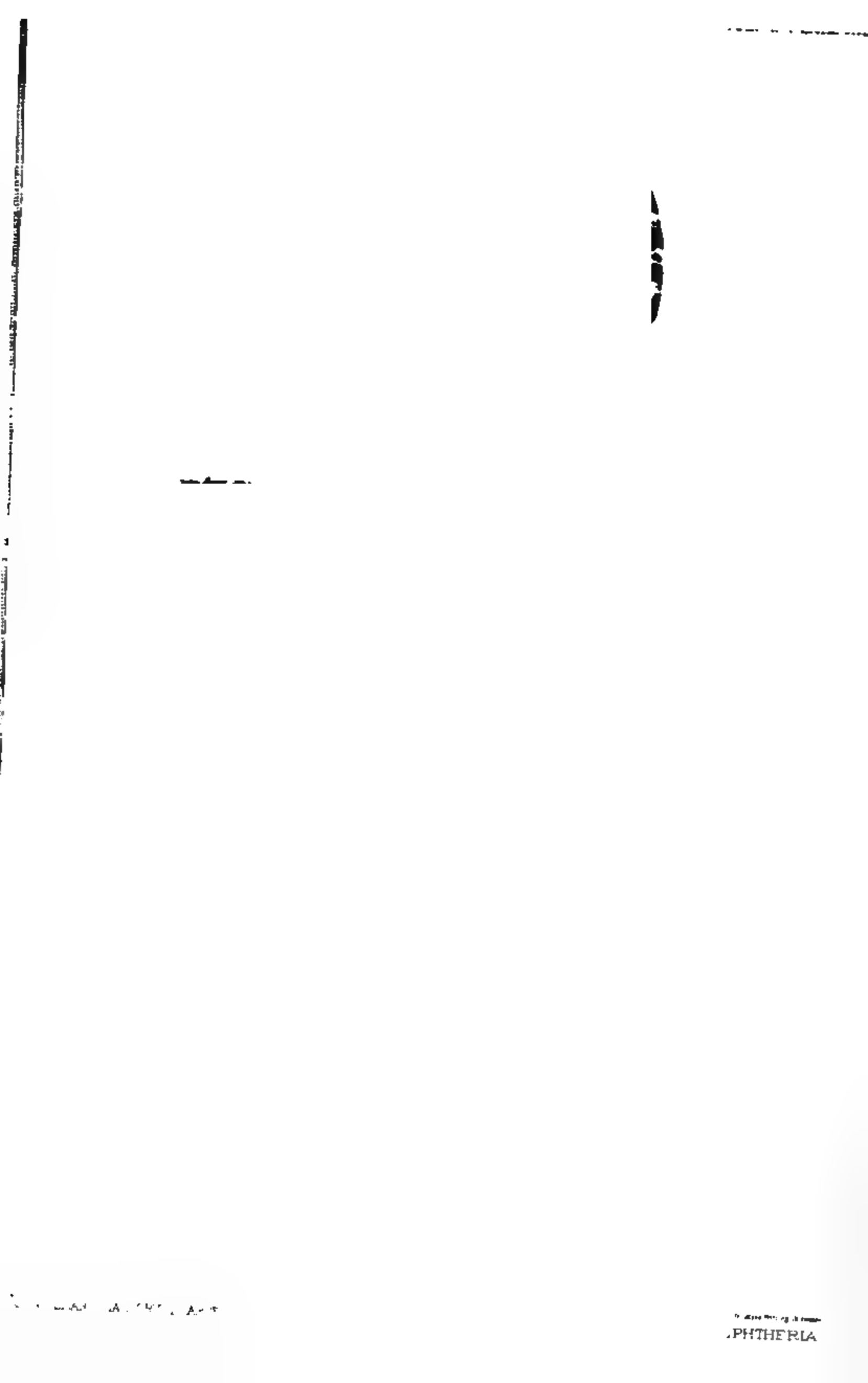




PLATE XXII.

FIGURE 1. — Section of myocardium, showing acute interstitial myocarditis.

FIGURE 2. — Section of liver, showing slight degeneration. The liver cells are swollen and contain large pale granules.

FIGURE 3. — Section of liver through an area of central necrosis. The liver cells are broken up, separated from their connections, and lie in large spaces. "a," liver cells. "b," walls of capillaries. "c," endothelial cell in capillary.

FIGURE 4. — Section of liver through central necrosis, showing capillaries between necrotic liver cells occluded by thrombi of fibrin.





PLATE XXIII.

FIGURE 1. — Focal necrosis of liver adjoining central vein of lobule. The small dark nuclei of the necrotic area represent polynuclear leucocytes which have invaded the necrotic liver cells. "a," focus of necrosis. "b," central vein.

FIGURE 2. — Degeneration of liver cells not so marked as in Fig. 2, Plate XXII. "a," endothelial cell. "b," endothelial cell enclosing a polynuclear leucocyte.

FIGURE 3. — Degenerated liver cells from an area of central necrosis. There is a wide space between the degenerated liver cells and the capillary walls. The endothelial cells of the capillaries are swollen and the vessels and spaces around the liver cells contain granular débris.

FIGURE 4. — From the same section as Fig. 3. The liver cells broken up into fragments. There are numbers of endothelial cells in the capillaries.

PLATE XXIV.

FIGURE 1. — Convoluted tubules of kidney, showing cloudy swelling. The cells are greatly swollen and the granules increased in size and number. The ciliated borders of the cells are irregular.

FIGURE 2. — Longitudinal section of ascending loop of Henle. The ciliated border and the granules at the base of the ciliæ are well shown. The cells are swollen, their texture much looser than normal, and the lumen contains granules probably derived from the cells.

FIGURE 3. — Sections of convoluted tubules. The cells more granular and so swollen as to occlude the lumen.

FIGURE 4. — Greatly degenerated convoluted tubule. The cells are greatly swollen; the granules, many of which are distinctly hyaline, lie in spaces in the cells. The lumen is completely occluded.

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PLATE XXV.

- FIGURE 1.** — Hyaline degeneration of proximal convoluted tubule. The cells contain large numbers of round hyaline droplets.
- FIGURE 2.** — Acute interstitial nephritis, circumscribed foci of interstitial infiltration with plasma cells chiefly beneath the capsule.
- FIGURE 3.** — Intense acute interstitial nephritis. The kidneys in this case were greatly enlarged. The dark color of the section is due to the great numbers of cells in the interstitial tissue.

PLATE XXVI.

- FIGURE 1.** — Acute intracapillary glomerulo-nephritis. The glomerulus is enlarged, the lobulation more evident than normal, and the capillaries contain few blood corpuscles and an increased number of cells.
- FIGURE 2.** — Early stage of acute intracapillary glomerulo-nephritis. There is slight increase in the capillary cells. "a," nuclear figure in cells within the capillaries.
- FIGURE 3.** — Glomerulus from an advanced case of glomerulo-nephritis. The glomerulus is lobulated and contains great numbers of cells. There is also a great increase of cells in the capsular space.
- FIGURE 4.** — Acute glomerulo-nephritis with exudation. The capillaries are bare of epithelium, and in places are necrotic. There is abundant hæmorrhagic and fibrinous exudation in the capsular space, and extending from this into the tubule.
- FIGURE 5.** — Acute glomerulo-nephritis. In the capsular space a dense mass composed of red blood corpuscles and hyaline fibrin. The vascular tuft necrotic.

$\psi = \frac{1}{\sqrt{2}}(\psi_A + i\psi_B)$, $\psi = \frac{1}{\sqrt{2}}(\psi_A - i\psi_B)$

Fig. 5

D FIFTH

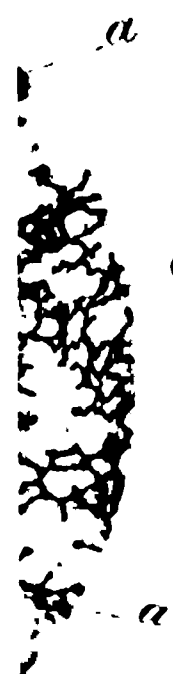


PLATE XXVII.

- FIGURE 1. — Bone marrow, showing the relative numbers of marrow and lymphoid cells. The small dark nuclei belong to lymphoid cells.
- FIGURE 2. — A part of same marrow highly magnified, showing the marrow cells.
- FIGURE 3. — Section of lung, showing 5 atria with cellular infiltration about them. No exudation in the other air spaces. "a," atrium.
- FIGURE 4. — Primary infection about atrium. "a," atrium. "b," air sac. "c," alveolus.
- FIGURE 5. — Primary infection of terminal bronchus and atria. "d," bronchus. "a," atrium. "e," artery accompanying bronchus.

PLATE XXVIII.

FIGURE 1. — Section of lung, showing several small foci of exudation affecting terminal bronchi and atria. “a” “a” “a,” terminal bronchi.

FIGURE 2. — Longitudinal section of terminal bronchus and bronchial passage, showing gradual downward extension of the exudation.

FIGURE 3. — Section of lung, showing infection of two terminal bronchi and the adjoining lung tissue. “a,” bronchus just above bifurcation. “b” “b,” terminal bronchi.

FIGURE 4. — Section through large area of complete consolidation. The opening in the centre represents a bronchus. There is fibrinous exudation in the surrounding air spaces, shown by the dark masses within them. In the lung elsewhere the exudation is cellular. “a,” artery accompanying bronchus with masses of fibrin in the lymphatics around it.

FIGURE 5. — Section of lung with serous and hæmorrhagic exudation in the air spaces. “a,” bone marrow cell in capillary.

a

Fig. 2

b

a

Fig. 4.



PLATE XXIX.

- FIGURE 1.** — Section of the lung from a case of interstitial pneumonia, showing great swelling and proliferation of the lining epithelium.
- FIGURE 2.** — Section of bronchus, showing hyperæmia of the wall, desquamation of epithelium, and a large exudation between the wall and the desquamated epithelium.
- FIGURE 3.** — Sub-pleural lymphatic with mass of newly formed connective tissue within it.
- FIGURE 4.** — Sub-pleural lymphatic filled with large endothelial cells and polynuclear leucocytes.
- FIGURE 5.** — Large masses of diphtheria bacilli completely filling the air spaces of the lung. The walls of the air spaces are represented by the clear spaces.

Fig. 1

Fig. 4

2011-11-11



PLATE XXX.

- FIGURE 1.** — A lobule of the lung completely solidified, with very slight exudation in the adjoining lobule. The interlobular septum contains fibrin. "a," lymph spaces in interlobular septum filled with fibrin.
- FIGURE 2.** — Small bronchus containing exudation, in the middle of which is a large mass of diphtheria bacilli.
- FIGURE 3.** — Small bronchus with exudation within it and cellular infiltration of the walls.
- FIGURE 4.** — Small bifurcated bronchus in the interior of area of pneumonia. The dark areas in the bronchi are composed of solid masses of diphtheria bacilli. The exudation in the lung is purulent.

SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society; the next will be held on February 19, at the Harvard Medical School, at 8 P.M.

All communications should be addressed to the Editor,

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MAY 18 1901

JOURNAL

OF THE

Boston Society of Medical Sciences.

VOLUME V. No. 6.

JANUARY 15, 1901.

Owing to the delays caused by the Heliotype Company, the plates of No. 5 of the JOURNAL are not completed. The number will be issued when they are delivered.

FROM THE ASPECT OF THE SUBJECT. THE VIEW GENERALLY accepted at present is that the members of the genus *Anopheles* are the intermediate hosts of the malarial parasites, and that the far more numerous species of the genus *Culex* are not transmitters of human malaria, but are intermediate hosts of avian malaria. Ross found *C. fatigans* the intermediate host of *Proteosoma grassii*, the tropical malaria of birds, while Koch traced the same relationship to *C. nemorosus* in Italy. Observers there have had only negative results with *Culex* fed with infected human blood. Though it was stated by Koch about a year ago that possibly *Culex* may also

transmit human malaria, I have seen no repetition of that statement. Thayer reports from Baltimore the appearance of parasites in several individuals of *A. quadrimaculatus* after they had been fed with malarial blood, both tertian and tropical.¹

If it should eventually be shown that malaria is associated with certain species of mosquitoes only, we shall have to agree with R. Blanchard when he states that henceforth the zoölogist will have a voice in determining the salubrity of any territory, especially when we bear in mind that Giles has recently described 222 species of mosquitoes. It cannot be said that the whole problem has yet reached a definite settlement, especially in our climate, where only tertian malaria prevails. We have still before us the important problem why tropical malaria does not take root among us, and therefore whether the transmitters of the three different races or species of malarial parasites are the same or specifically distinct.

Probably 90 per cent. or more of all the mosquitoes we encounter in our latitude belong to the genus *Culex*. The genus *Anopheles* is, however, not unrepresented. In a table compiled by Howard and Coquillett, *A. punctipennis* has been observed at Beverly and Cambridge in this vicinity, and at Middletown, Conn. *A. quadrimaculatus* has been seen at Berlin Falls, N.H., and at Middletown, Conn.

During the years 1899 and 1900 I paid more or less attention to the species which came under my observation on the grounds and in the buildings of the Bussey Institution, adjoining the Arnold Arboretum.

A. punctipennis was quite abundant in an abandoned room on a level with the ground, from September to November, 1899. During 1900 this species was quite rare, probably owing to the continued drought. One specimen I found as early as April, others in living-rooms during September, October, and November. The same species was brought to me from a house near Franklin Park, in which a case of malaria had occurred the year before.

¹ I can only agree with Koch when he suggests the use of the term "tropical" in place of the cumbrous and not universally applicable "aestivo-autumnal" of Italian investigators.

A. quadrimaculatus I found in my home in July and September of 1899, and in August of 1900. I found a specimen in my laboratory in September. I am inclined to think that in years of normal rainfall it will be found more abundant. Thus far this species has been the rarer of the two. Their breeding-places I do not know. I am, however, of the opinion that several small ponds in the Arboretum near the Bussey grounds harbor the larvæ.¹ In the near future the agency of small bodies of water in our public reservations in the dissemination of malaria will need investigation.

Of the genus *Culex* I have collected the usual assortment reported by observers elsewhere. The predominant species in the territory under consideration from July on is *C. pun-gens*. In other regions probably other species will be found in largest numbers. Thus near the eastern end of Cape Cod I found *C. perturbans*, a rather large, elegant species, in possession of the field early in July. The interested observer will also find after a little experience that the species caught in the woods or out of doors are not infrequently different from those that enter our houses.

The existence of *Anopheles* in any neighborhood naturally excites our curiosity concerning the incidence of malaria. The few families living in the territory explored by me have, so far as I know, been free from this disease, excepting the family mentioned above. This brings us to the second factor in the etiology. Since 1896 I have had the opportunity to examine for the Massachusetts State Board of Health a number of localities in which malaria had recently appeared or greatly increased in prevalence. I soon became imbued with the idea that malaria is introduced by human beings, and that the mosquito only becomes infected through its food obtained as blood from infected individuals. The Italian, English, and German investigators have taken the same ground as a result of their researches, and Koch goes so far as to maintain that the only feasible method of exterminating malaria is to suppress it in the human subject by appropriate

¹ Early in June, 1900, I received a specimen from a town in this State in which malaria had been very prevalent during the fall of 1899. It came from a dwelling in which a case of malaria had just occurred.

treatment. This theory I think will serve to explain why *Anopheles* may be present without doing harm. When, however, infected human beings come together as bands of laborers, huddled together in open camps at night near sluggishly-running or stagnant water, the conditions for an epidemic among them (unless immune) and the native population are at hand. It is interesting to note that although the territory under consideration has been the scene of much disturbance of the soil within the past four years, on account of the change of grade of a railroad and the construction of a large sewer, malaria has not appeared. This favorable showing is due, I think, to the scattering of the laborers after work hours. It should not be inferred, however, that laborers' camps are of necessity foci of malarial infection. The choice of a proper site for a camp, screening of doors and windows with netting, and the prompt treatment of malarial fever among such laborers, should succeed in suppressing the disease as well as it can be done in large tenement houses in any of our mill towns, which, as a rule, are well provided with streams, ponds, and even undrained marshes.

Thus the progress of medical science once again insists upon the important principle that the sanitary protection of a part of the community, however small, insignificant, or lowly, is essential to the safety and well-being of the whole.

To those who are interested in these insect pests I would recommend the study of a small territory, throughout the entire season if possible, as the best means of accumulating information useful both to themselves and to others. Breeding should also be attempted, at first of the easily bred species of *Culex*, then of the other genus if accessible.

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Ficalbi, E. Venti Specie di Zanzare (*Culicidæ*) italiane, etc. Florence, 1899.

Giles, G. M. A Handbook of the Gnats or Mosquitoes, giving the Anatomy and the Life History of the *Culicidæ*. London, 1900, 374 pp.

Howard, L. O. Notes on the Mosquitoes of the United States. (Bulletin of the U.S. Dept. of Agriculture. Washington, 1900.)

See also the various recent articles on malaria, for facts about mosquitoes.

NOTES ON ANOPHELES.

CHARLES SEDGWICK MINOT.

The following notes were contributed to a discussion of Dr. Theobald Smith's paper upon the mosquitos in the neighborhood of Boston, and are based upon observations made in 1879. At that time I was living in West Roxbury, a town now included within the limits of Boston; and I devoted during several summers much attention to the insect fauna of the fresh water. Among the many forms collected, one was found quite abundantly in the stagnant waters of the neighborhood, which especially attracted attention by its peculiar habit of feeding, for as it lay against the surface of the water, quite motionless, it would suddenly twist its head over, without changing the position of the body, until the head was upside down, — that is, the mouth would be facing the sky instead of the bottom of the pond. Immediately the insect would begin beating the water very rapidly with its oral appendages, which are armed with long, stiff, curving bristles, and thus create a current towards its mouth, and thereby bring particles which were floating on or near the surface to its mouth, where the particles could be seized and swallowed. The larvæ fed, so far as I observed, in no other way. The beating of the water would be maintained for a short time, not many seconds, usually, and the insect then turned its head back to the normal position, and after a short rest repeated the operations as before. Usually after feeding in this way for a few times the larva with a wriggle freed itself from the surface and made its way to the bottom of the dish, where it remained quiet for a while, and thereupon remounted to the surface to breathe and to feed again. The method of respiration is similar to that of the mosquito, there being a respiratory tube on the dorsal side of the ninth (eighth abdominal) segment, with two tracheal openings at its end, — see Plate XXXI., Fig. 2*a*. Sometimes the larva could be observed to thrust its head forward, thus revealing the long

and slender neck, which is hidden under the large first segment, when the animal is at rest. It is this long neck which renders possible the singular rotation of the head. Not knowing what this odd larva was, I designated it in my notes as "*head-turner*," and it seems to me that this would be a satisfactory popular name for it, and I therefore suggest its adoption.

I reared many of these insects to maturity, for they are easily kept in confinement. There should be some mud at the bottom of the dish, and green plants to freshen the water, the surface of which must be free from dust, otherwise the insects will be smothered. It was with no little surprise that I saw my head-turner transform into a mosquito. I took some of these specimens to Mr. Edward Burgess, who, though celebrated as the designer of three yachts of international fame, was equally remarkable for his knowledge of insects, and as a special student of North American diptera had made himself the foremost authority of his time upon this order. Mr. Burgess identified the mosquitos as *Anopheles*, but unfortunately could not then determine the species. As I soon withdrew from my entomological studies to devote myself more to embryology, my observations have remained unpublished. It is to be regretted that the adult specimens actually raised have been lost, so that I cannot now determine the species with certainty. I found two species of larvæ, but my drawings refer to only the commoner of these, which probably belongs to *Anopheles punctipennis*.

I am able by my own observations to confirm the very accurate account of the habits of the larvæ and pupæ of both *Culex* and *Anopheles*, given by L. O. Howard in Bulletin No. 25 (N.S.) of the U.S. Division of Entomology, but cannot add anything important.

Owing to the great interest attaching to the genus *Anopheles* the editor of the Journal has considered these notes worth publishing, since they record what are perhaps the earliest observations on the life history of these mosquitos. I am able also with the aid of the accompanying plates to point out certain distinctions between the larvæ and pupæ of

Culex and *Anopheles*.¹ Figs. 1 and 3 represent the larva and pupa of the same individual *Culex*; Figs. 2 and 4 of the same individual *Anopheles*. The *Culex* larva is a very characteristic species, which can, I think, easily be found again and reared for identification. It is green shading into brown, the intestine usually forming a dark band owing to the food with which it is gorged; the band extends through the second to ninth segments; the head is brownish yellow, the eyes a very dark brown; but the most characteristic feature is the *white* antenna, although at its base it is brown, and its terminal joint and setæ are also brown. This larva is a well characterized and easily recognized species. The *Anopheles* is, as said, probably *A. punctipennis*.

Comparison of the larvæ shows that the type is similar in the two forms, but there are many minor differences. The larva of *Anopheles* is larger than that of any *Culex* I have seen.

The head is much larger and broader in *Culex* than in *Anopheles*; the length is about the same in the two forms. *Culex* has a tuft of hairs at the base of the antenna, which project forward, and are nearly as long as the antennæ.

The antennæ in *Culex* are long and curving; in *Anopheles* they are shorter and straight.

The eyes in *Culex* are large and broad; in *Anopheles*, narrow and oblique.

The first² segment in *Culex* is nearly as long as broad; in *Anopheles* the breadth is much greater than the length, and as shown in the figures the lengths and the arrangement of the bristles borne by this segment are very unlike in the two genera.

The second to ninth segments are relatively broader in *Anopheles*, and the lateral bunches of long hairs which they bear gradually diminish in length from the second to ninth segment in *Anopheles*, while in *Culex* the hairs on the second to seventh segments are about of the same length, those on the eighth and ninth being much shorter.

¹ Whether the differences enumerated are all strictly generic must be determined by more extended observations.

² The segments, for convenience, are counted only as they appear in the drawings.

The respiratory tube is long, slender, and tapering in *Culex*, and in *Anopheles* is a short cylinder terminating in a blunt cone.

The tenth segment ends squarely in *Culex*, while in *Anopheles* it is rounded, and bears in addition a straight terminal spine beset with lateral hairs.

Many of these differences are clearly shown in Howard's figures, but his representations of the spines and hairs differ from what I have seen.

In regard to the pupæ, we have to do chiefly with differences in proportion, the pupa of *Culex* being much smaller and with a slenderer abdomen than *Anopheles*. The last abdominal segment in *Culex* is small, that of *Anopheles* forms a much larger cone. The respiratory tube arises from the thorax much higher up dorsally in *Culex* than in *Anopheles*. Possibly the differences in shape and length of the tubes are also of generic value.

In regard to the color of the *Anopheles* pupa figured, I give my notes, as they may assist the future identification of the species:

"Upper side of thorax and abdomen brown; lower side of thorax and abdomen, and anterior end of thorax, green. Seen from above, the pupa shows on each side of the thorax a glistening triangle, caused by air contained under the wing and between the legs; in the middle of the glistening triangle is a reddish brown dot; the middle lines of the thorax and abdomen are brown, but the edges of both parts appear green from above."

In regard to the malarial host I am able, then, to state that it was common in the stagnant waters of that part of Boston known as West Roxbury, according to observations, in 1878, '79, and '80. It is presumably equally common in that district at the present time. I found it in several localities, all low, swampy lands, in the neighborhood of Forest Hills. There may be specified as habitats the ditches at Woodbourne, and on the next estate, then belonging to Richard Olney, Esq., on the Bussey estate, now part of the Arnold Arboretum, and in one of the ponds of Mount Hope cemetery.

PLATE XXXI.

All the figures are magnified fifteen diameters, except Fig. 2*a*. They are reproductions of the untouched original pencil sketches, except Fig. 1, which is from a water-color drawing.

Fig. 1. Larva of *Culex*, sp.?

Fig. 3. Pupa stage of the larva of Fig. 1.

Fig. 2. Larva of *Anopheles* (? *punctipennis*).

Fig. 2*a*. More highly magnified view of the end of the respiratory tube of the same larva.

Fig. 4. Pupa stage of the larva of Fig. 2.

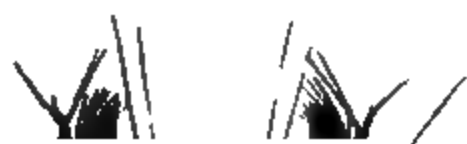


Fig. 1

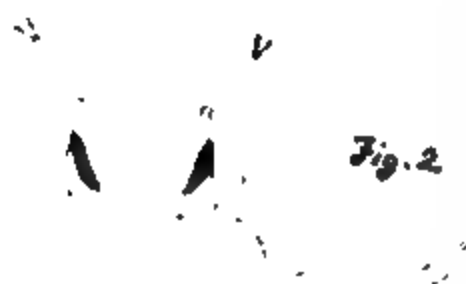


Fig. 2



Fig. 2a



Fig. 3



Fig. 4

.....

To raise the larvæ it is convenient to use small dishes, perhaps three inches in diameter and an inch and a half deep. If each larva is kept in a dish by itself, the identification of the stages and species can be made certain. The pupæ both of *Culex* and *Anopheles* hatch into the adult quite suddenly. The pupa rises to the surface when the time for transformation arrives, and remains quite motionless; the shell splits down the middle dorsal line of the thorax and spreads open; the perfect insect immediately slips out from the shell, and reposes upon it, resting its feet thereon, but usually remains only a few instants before flying off. Its first flight is apparently a perfect performance. The whole transformation occupies only a few seconds. To prevent the escape of the imago, the dish with the pupa should be covered with muslin or fine netting. If this is not done, the observations are likely to end in final disappointment.

NOTES ON MOSQUITOS TAKEN AT PROVIDENCE, R.I., IN 1900.

F. P. GORHAM.

(From the Anatomical Laboratory of Brown University.)

During the year 1900, in connection with the Health Department of Providence, an attempt was made to determine the species of mosquitos found in the city, and if possible to locate their breeding-places. In the time at our disposal we could make but an imperfect survey of the numerous ponds and swamps about the city, but a beginning at least was made, and another year it is hoped that a more complete and careful examination can be undertaken.

Adult mosquitos were found during every month of the year; in the winter months the majority of those captured were found hibernating indoors, but occasionally, on a warm day, a specimen would be taken out of doors. Search for larval mosquitos was not begun until August, but from August to December they were abundant. In the latter month many were found, though ice of considerable thickness had formed above them, and they could breathe only the air collected beneath the ice.

Before beginning our search for their breeding-places we supposed that every body of water would be found to contain more or less mosquito larvæ, but as the search went on we were surprised to find that in only a few of the ponds and streams in or near the city were mosquitos breeding. We soon came to the conclusion that the presence of fish of any kind in the water was a sure sign that there were no mosquito larvæ there. This of course is a valuable suggestion as to one of the methods to be employed in ridding a locality of mosquitos. Out of some ninety bodies of water carefully examined, but thirteen were found that contained larvæ.

One species (*Culex tæniorhynchus*, Wied.) was found breeding in a tide-pool of salt water where the density of the water was 1.028. This probably explains the origin of the enormous swarms of mosquitos that make life miserable on

many of the islands of Narragansett Bay during the summer months. Sewage, chemicals, and dye-stuffs in the water seem to make it especially favorable for the larvæ of *Culex pungens*, Wied. The great numbers of this species that infest the "East Side" of Providence probably come from the old Blackstone canal, the waters of which, though loaded with impurities of all sorts, are literally filled, during the summer and fall, with their larvæ. They are so abundant in parts of the canal that the color of the water is changed, and a quart jar of the water, scooped up at random, will have two solid inches of mosquito larvæ on the bottom.

The following species have already been identified from among those captured in 1900. Much of the material collected, however, has not yet been examined:

Culex pungens, Wied. The most common species. Taken in every month in the year. Found breeding throughout the summer and fall, even as late as December 15, in sewage, cesspools, and clear water everywhere.

Culex tæniorhynchus, Wied. Though abundant everywhere, is most common near the salt water. Was found breeding in August in the salt marshes.

Culex stimulans, Walk. Taken in May, August, September, and October. Quite common.

Culex impiger, Walk. Taken in May and August. Comparatively rare.

Anopheles punctipennis, Say. Was taken in September in a single locality. Was not found breeding.

BROWN UNIVERSITY, Jan. 17, 1901.

REPORT OF THE HISTOLOGIC CHANGES FOUND IN THE
TISSUES OF ANIMALS INOCULATED WITH DIPLOCOCCUS
SCARLATINÆ (CLASS).

E. R. LECOUNT.

(From the Pathological Laboratory of Rush Medical College.)

Presented to the Chicago Pathological Society, Jan. 14, 1901.

The animals inoculated by Dr. Class with pure cultures of diplococcus scarlatinæ include three pigs (swine) of which two were inoculated intravenously and one into the peritoneal cavity; one died at the end of a week, and two were killed on the thirteenth and fourteenth days respectively; three guinea-pigs inoculated in the peritoneal cavity died on the fourth, fourteenth, and seventeenth days. The organs of these animals were examined as well as those from a number of mice. Death took place in these last-named animals very quickly and the organs show practically no changes. Pure cultures of the diplococcus were obtained from the heart's blood and different viscera in every case. Bacteria were not found in any of the sections. It is possible that the diplococcus, which is polymorphous, could not be distinguished from chromatic granules. In the larger animals very definite changes are present in certain organs. In the livers of the pigs are focal necroses that are, however, always small: they occupy but a small part of the lobule and contain fibrin. The necrotic liver cells are replaced by accumulations of cells which are evidently leucocytes and many of them eosinophilous; in these accumulations a few cells are present that resemble plasma cells in morphology and staining reactions.

Often the clumps of cells within the capillaries block the channel without any observable changes in the adjacent liver cells; in places these accumulations are most marked near the central vein. Nuclei in karyokinesis occur in the endothelial cells lining the capillaries within lobules and in leucocytes. Very few cell inclusions occur.

In the liver sections of guinea-pigs similar changes are

PLATE XXXII.

FIG. 1. — Area of necrosis in liver of a guinea-pig with leucocytic accumulation. (Iron-hæmatoxylin staining.)

FIG. 2. — Area of necrosis in the liver of a pig with fibrin formation. (Weigert's fibrin staining.)

FIG. 3. — Cluster of large plasma cells in a sinus of the spleen of a guinea-pig. (Polychrome blue and eosin staining.)



FIG. 1.

FIG. 2.

FIG. 3.

DIPLOCOCCUS SCARLATINÆ (CLASS).

LECOUNT.

present. Many eosinophilous cells, a few cells resembling plasma cells, cells with pyknotic nuclei and small amounts of fibrin are found in the capillaries and small focal necroses of the liver tissue. In the Malpighian corpuscles of the spleens from swine dividing nuclei occur as well as occasional free chromatin granules. There are no necroses in the spleen, and such masses of fibrin as occur are in small vessels and have every appearance of post-mortem clots. In the spleens of guinea-pigs similar changes occur; plasma cells are very abundant in some sinuses; phagocytic cells or cell inclusions are not rare, plasma cells often fill the sinus.

The lymph glands from the swine show no histological changes that can be considered abnormal, with the exception of enlarged nodules, lymph sinuses that are packed with cells, an abundance of multiplying cells in the germinal centres, and in one animal small amounts of fibrin within the sinuses.

In the kidneys of the swine, the only change is swelling of the epithelium, and this is not marked; in the kidneys from the guinea-pigs, the epithelial swelling is more marked and a few hyaline casts occur. The other organs examined, viz., the lungs, heart, stomach, intestines, thymus, and bone marrow, show no changes. In the adrenal of a guinea-pig beautiful minute focal necroses occur similar to those in the liver, and in the skin of a pig the seat of a rash engorgement of the blood vessels is present.

It is obviously of doubtful value to compare the histologic changes in these few animals with the elaborate study by Pearce¹ of the minute anatomy of human scarlatina; yet it is evident that these changes here reported differ from the alterations described by Pearce in degree rather than character. One chief difference is in the lack of lesions in the kidneys in the animals in comparison to the changes in this organ in scarlatina. There is a similar hyperplasia of lymphoid tissue, focal necroses, and the occurrence of plasma cells in situations that betoken their presence in the circulating blood.

¹ Medical and Surgical Reports of Boston City Hospital, 1899, xi, 39-82, and Journal Boston Society Medical Sciences, vol. iii, p. 161.

ACTION OF THE LARYNX IN RELATION TO THE PITCH OF
THE VOICE.

THOMAS FILLEBROWNE.

The relation of the human larynx to the production of voice has made it an object of deep interest to the physiologist from early times. While its anatomical construction has long been clearly understood, its physiological action has always been a matter of discussion. On this point opposite opinions still prevail. The purpose of this paper is to present a few results derived from a study of the movements of the larynx in respect to the pitch of the voice, in the hope that these results may contribute somewhat toward a settlement of this question.

Until recent years the prevailing opinion among scientists has been that in normal action the larynx rises with each higher pitch of the voice, and falls with each lower note produced. On the contrary, many practical singers and speakers are convinced from long observation that the best vocal results are obtained if the position of the larynx be allowed to remain unchanged when the pitch of the voice is raised or lowered. With this last conclusion some, however, do not agree.

The first steps in our inquiry should be, if possible, to determine the normal condition and action of the larynx.

"Nature" and "natural action," which are so often quoted as illustrations, cannot, in this case at any rate, be relied upon. A new-born child is little more than a bundle of possibilities to be developed by training. The functions of organic life are the only ones that are sure to be performed correctly.

All other capabilities that reveal themselves with advancing years spring from training; and this training is largely a matter of imitation. The child utters the same sounds and speaks the same language with the same national inflections that it hears on every side. Its gestures and grimaces are

but copies of the movements that it sees in older people. In thus reproducing speech and gesture the child never reasons about the correctness of one or the grace of the other. It proceeds on the unconscious assumption that whatever it hears and sees is right, and it employs every power to adjust itself as accurately as possible to its environment.

If the child should be so happily situated as to grow up in daily contact with a correct speaker possessed of a musical voice, these good qualities will perpetuate themselves in the child by unconscious imitation. If, on the contrary, it hears only harsh voices, vicious pronunciations, and slipshod constructions, accompanied by awkward gestures, the child just as surely assimilates these disagreeable qualities.

The Romans recognized the importance of good example in this respect, for Quintilian says: "Before all, let the nurses speak properly. The boy will hear them first, and will try to shape his words by imitating them." More than three centuries ago Roger Ascham declared: "All languages, both learned and mother tongues, are begotten and gotten solely by imitation. For as ye used to hear, so ye learn to speak. If ye hear not no other, ye speak not yourself."

It would appear, then, that the movement of the larynx is controlled largely by the imitative faculty. If this is true, then it is also obvious that the proper action of the organ cannot be ascertained from an examination of any subject taken at haphazard, but only from the qualities of the results obtained by an educated and well-trained voice. Both my experience and observation prove the action of the larynx to be as follows:

In ordinary conversation the larynx remains nearly still, in its normal position of rest, moving a little when compelled by the movements of the tongue in articulation.

In formal public speaking the larynx is carried forward and downward, which gives a larger and fuller tone.

In singing, the larynx assumes a still lower position, and is thrown forward, though not enough to induce any restraint. As the pitch of the voice is lowered, the throat is opened wider, and the larynx is depressed and held more

loosely. As the pitch of the tone is raised above the medium tone, the mouth is opened wider, the tongue descends, and with it the larynx, until at the highest note the larynx is at its lowest possible position consistent with ease and freedom.

The following quotations show the gradual change of opinion upon the subject:

L. Hermann, Professor of Physiology in Königsberg, voices the scientific opinion of continental Europe in his "Lehrbuch der Physiologie," 10th edition, page 343.

He states: "Bei Singen hebt sich der Kehlkopf um so mehr, je höher die töne sind." "In singing the larynx rises with the height of the tone."

In 1844 Professor Merkel wrote that, "The larynx ascends in the elevated tones; in the low tones, on the contrary, it is depressed."

In 1880 Emil Behnke stated that, "The voice box rises gradually with each higher note."

In 1892 Griffiths made this statement: "If, when the high note is sung, the larynx does not rise with the voice, but remains low down in the throat, the singer has at once attained the right mechanism."

In 1893 Mme. Medini gave this counsel: "In ascending the scale, open the throat a little wider as you ascend, but let it be always downward, as if to enlarge the larynx and the windpipe."

In these statements, covering a period of more than fifty years, it will be noticed that the earlier writers represent the larynx as rising and falling with the pitch of the voice, but that the later writers take an opposite view. This shows that recent observation has tended to reverse the opinions formerly held.

In order to ascertain the trend of opinion at the present time, the following questions were addressed to a number of singers and speakers resident in New England.

Answers were received from twelve persons.

Nine of these were teachers of singing, two of elocution, and four were vocalists. This number is large enough to indicate the prevailing opinion.

1st. When producing tone in the middle range of the voice, should the larynx rest at its lowest easy position as in yawning?

The answer to this question was a unanimous affirmative.

2d. When the voice runs down the scale from the medium notes, should the larynx change its position with each note? If so, should it rise or fall?

Nine thought the larynx should not change its position downward as the pitch of the voice was lowered.

Three thought it should go down a little with each lower note.

3d. When the voice ascends the scale should the larynx change its position? If so, should it rise or fall?

Eight thought the larynx should not rise when the voice ascends. Four believed it should rise with the pitch of the voice.

4th. Should the same conditions as to position of the larynx exist in speaking as in singing?

Nine agreed that the conditions governing singing and speaking were the same. Three thought the conditions were not the same.

The opinions of the teachers of singing were more sharply defined than those of the teachers of elocution. This is natural since speakers use only the medium range of pitch, while singers use also the extremes. In elocution the larynx needs little attention. The majority of teachers are inclined to think that the less the attention of the pupil is called to it the better. One who is credited with considerable ability as a teacher of elocution and who has attained a reputation as such, said that in teaching he had never given this subject any attention. Finally, however, he made the statement that "in proportion as the person is educated in vocalization, the larynx is depressed as the pitch of the voice is raised."

I also offer the evidence of my own experience. When a lad in my teens I heard or read the statement that the larynx should rise with the pitch of the voice, and I took great pains to apply it. I followed these teachings until, in early manhood, I was obliged to give up singing on account of throat

and bronchial irritation, and my speaking was laborious and voice limited.

About fifteen years ago I commenced study and practice according to the opposite rule, with the result that my voice has constantly increased in carrying power and in volume. Throat irritation is entirely gone and only a slight bronchial secretion occasionally appears to remind me of my once disabling infirmity.

I have invariably found that the lower down and farther forward my larynx is held without constraint, the better the tone in every quality. These observations were made by sensing the movements and position of my larynx while speaking or singing, and by verifying my sense by observing these movements and positions in the mirror.

Examination must be confined to outward observation of the larynx as indicated by the prominence of the thyroid cartilage, as the slightest mechanical interference either of touching externally or the use of the laryngoscope will so disturb the nervous force that the action cannot be normal or constant.

During the last five years I have particularly observed many singers as well as speakers, and invariably quality and control of the voice was commensurate with the completeness with which the larynx was allowed to rest low down in the throat.

I was granted an interview with the members of the choir of the New Old South Church and also with the Arlington Street Church choir.

The unanimous testimony of the Old South choir was that the larynx did not rise with the pitch of the voice. My observation of their singing showed plainly that this was the case. It could not possibly be otherwise, for invariably as the pitch was raised to the higher notes, the mouth was opened wider and the throat enlarged, which of necessity carried the back of the tongue downward and with it the larynx. The known ability of these singers and the excellence of their performance makes their opinion on the subject of much importance.

The views of the Arlington Street choir were not so definite. Two were emphatic in their opinion that the larynx should not rise with the pitch of the tone, but the reverse. One had never considered the position of the larynx and could not express an opinion as to the position of her own. Observation showed that when she sang the higher notes of the scale her mouth opened wider, her throat enlarged, and her larynx rested at its lowest easy position. The fourth member thought the larynx should rise with the pitch of the voice, and he sings according to that theory.

The writer has repeatedly noticed that naturally good singers and speakers who have habituated themselves to an improper movement of the larynx have failed in their vocal powers long before their years would warrant, or their physical strength has become impaired. Pitiable examples of the truth of this statement are not rare.

On the other hand, those who have throughout their lives practised the latter modern method retain their vocal powers as long as physical strength lasts, and are able in their very last days to sing and speak with ease, melody, and strength.

A PORTABLE DRY SPIROMETER.

G. W. FITZ.

There are in use at present two types of spirometer: the one the standard form of wet spirometer, which is merely a modification of a gasometer; the other the so-called dry spirometer, which consists of a collapsible cylinder of rubber cloth. Both have a capacity of about three gallons and are so large and cumbersome that they are seldom used except for the study of chest capacity in gymnasia.

In the hope of obtaining a light, portable spirometer for studies for which the more cumbersome forms were unavailable, the general plan of the Chinese paper lantern was adopted. Thin rubber cloth was cut into twelve disks eight inches in diameter, each with a one-inch hole in the centre. These disks were cemented together alternately by their outer and inner edges to form a bellows which, although perfectly flat in a collapsed state, is yet capable of extending to a height of ten inches with a capacity of five litres. Two disks of aluminium were then cemented and fastened by screw collars, one to the top, the other to the bottom of the bellows. The lower disk carries the inlet tube, the upper the index tube which stands vertically over the centre as in the ordinary form of dry spirometer. The spirometer was graduated by introducing measured amounts of air. Four small tubes which slip into receptacles in the base disk serve to guide the bellows, as does also a bridge of aluminium wire connecting the tops of two of these uprights and guiding the graduated stem by means of a loop at its middle.

By experiment it has been found that the registration of this spirometer compares favorably with that of the standard wet spirometer. Its lightness, its small bulk when collapsed (a cylinder nine inches in diameter, one inch in height), and the ease and rapidity with which it can be set up ($\frac{1}{2}$ minute) and used, are the advantages which make it available for bedside studies in such diseases as pneumonia, pleurisy, empyema, and tuberculosis.

A QUICK AND SIMPLE METHOD FOR FIXING THE BLOOD CORPUSCLES FOR DIFFERENTIAL STAINING.

W. F. WHITNEY.

Several methods for fixing blood smears without the delicate and rather tedious process of high heating have been proposed from time to time, but they are all uncertain. The following has never failed as yet in my hands when the blood is well spread and reliable stains are used.¹ It has the further advantage that heat is not required at any stage of the process, and the mounted specimen can be ready for examination within four minutes from the time the blood is drawn.

It consists simply in allowing a modified Zenker's fluid,² in which 5 per cent. of strong nitric acid is substituted for the 5 per cent. glacial acetic, to act for a few seconds.

The blood is drawn and spread in the usual way and dried thoroughly in the air, or if preferred by a gentle heat. The cover glass is taken with the forceps, the prepared surface covered with a few drops of the fluid and held while twenty are counted slowly. It is washed off with running water, blotted, covered in the same way with the triacid stain, which is allowed to remain for three minutes, washed as before, blotted thoroughly, dried, and mounted in xylol balsam.

The action depends upon the combination of corrosive sublimate with nitre and chromic acid which are formed in the solution, since satisfactory results were obtained by a mixture of 1 per cent. chromic acid with equal parts of a saturated solution of nitre and corrosive sublimate; but for practical use the original way seems to be the best.

Unna's polychrome methylene blue and Chezinski's eosine

¹ The Erlich triacid stain prepared by the apothecary of the Massachusetts General Hospital, and that by Grüber, to be obtained of Queen & Co., Philadelphia, are recommended.

² Zenker's fluid. Bichromate of potash 2. Sulph. soda 1. Water 100. This is saturated with corrosive sublimate while warm. Five per cent. glacial acetic acid added at time of using.

and methylene blue mixture both work well after this fixation. But Loeffler's blue gives a fine precipitate on the red corpuscles, due probably to the fact that the acid has not been thoroughly neutralized. This occurs in a very regular manner, and may explain appearances which have been regarded as due to granular degeneration of these corpuscles.

SECTION OF BACTERIOLOGY AND CHEMISTRY OF THE
AMERICAN PUBLIC HEALTH ASSOCIATION,
INDIANAPOLIS, OCT. 22-24, 1900.

*Some Observations on Methods for the Detection of B. Coli
Communis in Water.*

E. E. IRONS, Chicago.

The relative value of four methods was studied: (1) dextrose fermentation tube; (2) lactose fermentation tube; (3) carbol-broth method; (4) the lactose plate. The most approved method for the preparation of media in each case was used.

Approximately 1,100 determinations were made by the fermentation tube with dextrose and lactose. Lactose was used in the hope that the trouble caused by *B. cloacæ* might be avoided, but it was not found an advantage. The use of lactose was shown to give the most uniform results. Attention is also called to the fact that highly polluted waters frequently give very little gas formation, and that this may be avoided by the use of dilutions of the water.

A comparison of the carbol-broth method and dextrose fermentation tube in polluted and relatively unpolluted waters showed that the carbol-broth method gives a larger number of positive determinations for polluted waters. On the other hand, with relatively pure waters the dextrose tube is shown to be much more delicate than the carbol-broth method.

The use of lactose plates controlled by the dextrose fermentation tube showed that it was unreliable by not developing red colonies when the tube showed fermentation and by having an overgrowth of red colonies. The following conclusions are reached: First, when the dextrose tube method gives approximately 33 per cent. of CO_2 , *B. coli* is almost invariably present. Second, for the direct inoculation of water the dextrose fermentation tube is preferable to the lactose tube. Third, for polluted waters incubation in carbol-broth followed by lactose plate rather than the dextrose tube, while for

relatively pure waters the dextrose tube appears to be the most delicate. Fourth, for direct inoculation of highly polluted waters the lactose plate is less successful than either carbol-broth or the dextrose tube.

Variation of the Properties of the Colon Bacillus, isolated from Man.

W. W. FORD, Montreal, P.Q.

Ford reviews the important literature relating to this species. In his work he subjected all of the cultures of the typhoid-colon type to the procedures as used by Fuller and Johnston in their study of Ohio river bacteria. Preliminary cultivation for three days in broth, three days on gelatine plates, and three days on slant agar was made; after which various media were seeded and the observations recorded on charts by the + or — sign. By this means the various cultures at hand were separated into types that gave characteristics that remained distinct and, although not widely different, did not assume the characters of the other types. As special points noted during his studies Ford remarks: — Motility: Although disputed, a twenty-four-hour fluid culture of this class of organisms has never failed to show motility and he agrees with others that permanent absence of motility must be considered as a radical departure from the pure colon type. Gas production: Media containing sugars should not be sterilized in the autoclave for fear of altering the sugars. It is essential in studying colon that dextrose, lactose, and saccharose be used, as certain varieties ferment one and not the others, only the colon and its near allies ferment all three. Indol: This test has not yielded satisfactory results. The use of large amounts of sugar-free broth after 15 to 20 days' incubation may give good results, when this is distilled and the distillate tested for indol. Nitrites: Dunham's solution is recommended, or a nitrate broth using Dunham's solution as a control. Growth on agar: It was observed that agar of a reaction 1.5 per cent. acid gave most abundant growth.

Neutral agar gave a less growth, and agars of alkalinity up to 6 per cent. showed a gradual diminution.

The grouping of the organisms is into colon A, B, C, D, and E. Form A is accepted as typical *B. coli*; form B like A, but not producing scum on broth; colon C includes forms that ferment dextrose and lactose, but not saccharose. D includes forms like C, but not producing scum on broth. E represents a non-pathogenic form isolated by Ford. Under pasocolon A is included the hog cholera group and *B. icteroides* and bacilli studied by Burham and Basemen. Pasocolon B is a bacterium isolated by Ford and agreeing closely with *B. icteroides*. Characters of *B. typhosus* and *B. cloacæ* are also added in the table.

THERMAL DEATH POINT OF THE TUBERCLE BACILLUS AND
ITS RELATION TO THE PASTEURIZATION OF MILK.

H. L. RUSSEL AND E. G. HASTINGS, Madison, Wis.

Cultures of *B. tuberculosis* from three different sources were used. They were grown on dog's blood serum, and the mass of bacilli was ground up in normal salt solution. The resulting cloudy mixture was added directly to fresh milk. Pasteurization was accomplished in a 50-gallon rotating commercial pasteurizer. The milk containing the bacilli was placed in glass tubes closed by corks and protected by rubber. The tubes were removed at varying intervals, and from 1 to 2 cc. of the infected milk injected intraperitoneally in a guinea-pig.

In five series of experiments it was shown that all tubercle bacilli were killed by a 10-minute exposure to 60° C. The controls caused active tuberculosis.

The relative efficiency of pasteurization in bottles or open vessels and in the rotating pasteurizer is also shown. The two series of tests show the milk in the pasteurizer to be completely sterile after 10 minutes' exposure in the bottles; 10 minutes in one series and 15 minutes in the other did not render the milk innocuous. The practical deduction made is that pasteurization in open vessels should be discouraged. The authors agree with Smith that the formation of flocculent particles and "skin" protect the living bacilli so that they are not acted on so readily by heat.

A NOTE ON THE DISINFECTANT AND DEODORANT
PROPERTIES OF AMMONIUM PERSULPHATE.

M. P. RAVENEL AND S. H. GILLILAND, Philadelphia, Pa.

B. prodigiosus on glass rods was killed by 2.5 per cent. solution in 60 minutes, and by 5 per cent. solution in 30 minutes. On paper a like result was noted. *B. diphtheriæ* on glass rods was killed by 2.5 per cent. solution in 90 minutes, and by 5 per cent. solution in 40 minutes. The results on paper were identical.

A 2.5 per cent. solution killed *B. typhosus* on rods in 120 minutes; on paper, in 120 minutes. A 5 per cent. solution killed it on rods in 70 minutes; on paper in 60 minutes.

Anthrax spores, on silk threads, were killed in 21.5 hours by 2.5 per cent. solution, and in 13 hours by a 5 per cent. solution.

The deodorant power of the salt was tested on putrefying mixtures of blood. We found that 80 cc. of a 5 per cent. solution were required to deodorize a litre of such material, the process being complete in 30 minutes. A marked decrease of odor was noted, however, at the end of 10 minutes.

AN INQUIRY INTO THE ROLE OF THE DOMESTIC ANIMALS
IN THE CAUSATION OF TYPHOID FEVER.

WM. R. STOKES AND JOHN S. FULTON, Baltimore, Md.

For purposes of isolation of the typhoid bacillus from animal feces Hess's medium was used. The authors found it satisfactory. The first series of animals consisted of two chickens, two white rats, and a calf six weeks old. One-half litre of a 48-hour typhoid culture was given the calf in milk; the chickens and rats were fed with grain and bread moistened with the bouillon. No typhoid colonies were found by Hess's medium. A pig was next fed with one litre of a 24-hour typhoid bouillon each day for one month. The feces were plated daily with negative results as regards typhoid. Three days after the last feeding the pig was killed and cultures made from the organs. These were negative except for a few colonies of typhoid from the liver. Experiments with two rabbits and two guinea-pigs gave a similar result. The last experiment was on a pig fed with one litre of typhoid bouillon daily for one month. The feces and urine were examined daily with negative results. Serum tests with the blood of this pig showed a reaction of 1 : 20 at the end of the month. By subcutaneous injections the blood of this same pig now reacts 1 : 4000. The feeding of *B. typhoid* had no effect upon the temperature. The general conclusion is reached that the dejecta of animals play no considerable part in the distribution of typhoid fever.

SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society; the next will be held on **February 19**, at the Harvard Medical School, at 8 P.M.

All communications should be addressed to the Editor,

HAROLD C. ERNST, M.D.,

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688 Boylston Street,

Boston, Massachusetts, U.S.A.

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Boston Society of Medical Sciences.

VOLUME V. No. 7.

FEBRUARY 19, 1901.

THE RELATION BETWEEN CONDUCTIVITY AND THE
INORGANIC SALTS OF THE NERVE.¹

ALBERT P. MATHEWS.

(From the Laboratory of Physiology in the Harvard Medical School.)

A. The Chemical Stimulation of Nerves.

The following results were obtained in a large number of experiments on the sciatic nerve of the frog:

1. All neutral salts, except sodium salts and magnesium sulphate, require a minimum strength of solution of about fourteen atmospheres' osmotic pressure to stimulate the nerves of December frogs.

The salts examined were KCl, KBr, KI, KNO₃, KClO₃, K₂SO₄, KHSO₄, K₂Cr₂O₇, MgCl₂, MgSO₄, Mg(NO₃)₂, BaCl₂, Ba(NO₃)₂, CaCl₂, Ca(NO₃)₂, SrCl₂, Sr(NO₃)₂, LiCl, AgNO₃, CuCl₂, CuSO₄, ZnSO₄, NH₄, NO₃, (NH₄)₂SO₄.

2. All non-electrolytes tested, *i.e.*, glycerine, urea, glucose, and cane-sugar, require a minimum pressure of fourteen atmospheres to stimulate December frogs.

3. The apparently exceptional position of MgSO is probably due to the formation of double molecules reducing its

¹ The full account of these observations will appear in the American Journal of Physiology.

osmotic pressure below that calculated from its electrolytic dissociation.

4. The mineral acids, hydrochloric and nitric, will stimulate in $\frac{1}{5}$ N solution, H_2SO_4 in $\frac{2}{5}$ N, acetic acid in $\frac{7}{5}$ N, oxalic acid in $\frac{1}{7}$ N, lactic questionable, and phosphoric not at all. The acids hence stimulate in solutions with a somewhat lower osmotic pressure than the neutral salts. This is probably due to a specific stimulating action of the H ion.

5. The hydrates, NaOH , $\text{Ba}(\text{OH})_2$, KOH , will all stimulate in $\frac{1}{20}$ N solutions. In other words, the hydrates stimulate by means of the hydroxyl ions they possess. NH_4OH will not stimulate the nerve at all. This is due to the fact that the NH_4 ion is exceedingly poisonous, and NH_4OH is hardly at all dissociated, so that there are few OH ions present.

6. All salts which are hydrolytically split, yielding hydroxyl ions, are somewhat more efficacious than the neutral salts. This is due to the stimulating action of the hydroxyl ions formed, and their activity depends on the degree of hydrolysis present. The salts thus tested were Na_3PO_4 , Na_2HPO_4 , Na_2CO_3 , NaHCO_3 , $\text{NaC}_2\text{H}_3\text{O}_2$, $\text{Na}_2\text{C}_2\text{O}_4$, KC_2O_4 and sodium citrate.

7. The sodium salts tested, *i.e.*, NaCl , NaBr , NaI , Na_2SO_4 , NaHSO_4 , Na_2CO_3 , NaHCO_3 , Na_3 citrate, Na_3PO_4 , Na_2HPO_4 , NaH_2PO_4 , $\text{Na}_2\text{Cr}_2\text{O}_7$, NaCrO_4 , NaClO_3 , NaCH_3CO , $\text{Na}_2\text{C}_2\text{O}_4$, Na tartrate, Na arsenate, $\text{Na}_2\text{B}_4\text{O}_7$, at a temperature of 13° differ from all other compounds in that if the nerve is immersed in them, the muscle will contract even if the solutions have an osmotic pressure of five atmospheres (the nerve's pressure) or even less. The alkaline sodium salts, such as sodium acetate and oxalate, are more efficient than the others. Of the neutral salts the sulphate is very strong; the nitrate, iodide, bromide, and bichromate follow after.

8. The latent period observed for nearly all the non-electrolytes examined and for all electrolytes except sodium compounds is almost always less than ten minutes, and is in approximate ratio to the speed of diffusion of the compounds. Thus, K salts generally have a very short latent period, due to the K ion, Li salts have long latent periods,

due to the small velocity of the Li ion. Sugar has a greater latent period than glycerine.

9. The sodium compounds exhibit a peculiar relation in this respect. In solutions having an osmotic pressure of 14 atmospheres or more the latent period is short, from 1 to 6 minutes, and is intermediate between K and Li, corresponding to the intermediate speed of the Na ion. At a pressure of less than 14 atmospheres there is an abrupt change to a latent period of from 20 minutes to 2-3 hours.

10. A careful comparison of isosmotic solutions of NaCl with KCl, MgCl_2 , BaCl_2 , CaCl_2 , Na_2SO_4 , KI, NaBr, $\text{Mg}(\text{NO}_3)_2$, sugar, and glycerine on the two nerve preparations of the same frog shows no constant difference in stimulating action, beyond a difference in length of latent period and vigor of contraction, differences probably correlated with the speed of diffusion of the substances and not due to any specific action on the nerve.

These results show a remarkable uniformity between widely different salts in their stimulating action. Non-electrolytes without exception and all neutral salts which stimulate within ten minutes after immersion require a minimum osmotic pressure of fourteen atmospheres for stimulation. This demonstrates that such salts do not chemically stimulate the nerve, but stimulate it by drawing water from it. Whether this passage outward of water generates the nerve impulse directly, whether it brings about a change in the state of the protoplasm, such as that described by Darwin in the glands of *Drosera*, and this change sets up the impulse, or whether it increases the concentration of the organic constituents and ions at some point, is not as yet clear.

This change in the state of the nerve, whatever its nature, would appear to be produced with much greater ease by the OH, and somewhat more readily by the H ions.

The sodium salts stand as exceptions to the general rule just stated, that neutral salts stimulate osmotically. These compounds will all stimulate, even though they be in solution having an osmotic pressure equal to the nerve itself. Loeb's discovery of the muscle stimulating action of sodium ions

arouses suspicion that the stimulations observed may be due to the action of the sodium salts on muscle, instead of the nerve, by diffusion along the nerve into the muscle. That this may be true is indicated by the following facts:

In the weak solutions the latent period is very long (twenty minutes to three hours) and it bears a definite relationship to the speed of diffusion of the salts. The sudden lengthening of the latent period on passing from a solution having an osmotic pressure equal to the minimum stimulating solution of all other neutral salts to a solution of lower osmotic pressure is suggestive of a difference in the manner of action in the two cases. The sodium salts are efficient in the same order as observed by Loeb for muscle. No negative variation is to be detected in the nerve during muscle contraction in the weak solutions, but is apparent in the strong. If only the central third of the nerve is immersed in the solution the latent period is two to three times as great as it is when the whole nerve is immersed. This would be expected if the stimulation is muscular. The muscles continue to contract by individual fibrillar contractions for hours in weak solutions, as they do when immersed in sodium salts.

I conclude that in these weak solutions we are probably dealing with chemical stimulations of the muscle, not of the nerve, and that it is impossible to stimulate nerves chemically except by hydroxyl and hydrogen ions. All other apparent stimulations are due to the osmotic pressures of the salts.

B. Action of Inorganic Salts on Conductivity.

Solutions isotonic with the nerve give the following results:

All sodium salts except the strongly alkaline salts preserve nerve irritability for many hours. The acetate with a minimum quantity of hydroxyl ions is the best preservative. The oxalate, carbonate, bicarbonate, and citrate form too many hydroxyl ions and kill the nerve. All other than sodium salts kill the nerve with varying speeds, NH_4 compounds and K compounds being most poisonous. Mg, Ca, Ba, and Sr salts are less poisonous, but in the course of five to ten hours at 13° all prevent the generation of nerve

impulses. The speed of killing is proportionate to the speed of diffusion of the salts of the same group. If not too long exposed, the nerve apparently killed by KCl or MgCl_2 may be completely restored by NaCl. MgSO_4 solutions are less poisonous than MgCl_2 .

For the maintenance of irritability of the nerve Na compounds are necessary. Thus far no relationship has been found between the relative speeds of the anion and kation and the efficacy of the salt in the conduction of the nerve impulse. Experiments with mixtures have not yet been tried.

C. The Action of Curare.

The drug curare, as is well known, prevents the passage of the nerve impulse from the nerve to the muscle. It is supposed to act on the end of the nerve in the muscle. No explanation has been given, so far as I can find, of the manner in which the drug acts. In the course of this investigation, it was seen that although all other than Na compounds require a solution of high osmotic pressure to stimulate the nerve, the Na salts will cause contraction of the muscle in solutions isotonic with the nerve. For the reasons already given, it seems to me that these contractions are due to the passage of the Na ions down the nerve into the muscle, and not to nerve impulses generated by the action of the salt on the nerve. If this were the case, I expected curare, which blocks the nerve impulse, would stop contractions in strong but not in weak solutions. This did not prove to be the case. Curarized muscle, although readily contracting if immersed directly in solutions of sodium salts, never contracts, so far as I have observed, if the nerve only is immersed in the salt. This observation, which confirms Limbourg, demonstrates, if the previous inference is correct, that curare blocks the passage of Na ions from the nerve into the muscle—in other words, that it renders the end of the nerve a semi-permeable membrane not permeable for Na salts. The following facts seem to be established:

(1.) Any relative increase of the Na ions in muscle at any

place sets up a change which is propagated through the muscle and causes contraction.

(2.) Curare blocks the passage of the nerve impulse from the nerve to the muscle.

If the interpretation already given be correct, we can add to these two facts the third:

(3.) Curare blocks the passage of Na ions from the nerve to the muscle.

DERMATOMYOSITES, WITH REPORT OF A CASE WHICH ALSO
PRESENTED A RARE MUSCLE ANOMALY, BUT ONCE
DESCRIBED IN MAN.

(*Abstract.*)

WALTER R. STEINER, A.M., M.D.

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Although myosites has been long recognized, yet a multiple muscle inflammation, presenting also other well-known symptoms, was not described as such until 1887. In that year E. Wagner of Leipzig, Unverricht of the Polyclinic at Jena, and Hepp of Kussmaul's clinic at Strasburg, almost simultaneously reported a case. Unverricht's case was also described seven years previously by Marchand, and Henry Jackson of Boston published a short account of Hepp's case in 1887. Since then over thirty cases have been reported, but a careful analysis of them will reduce this number to seventeen. They are classified according to countries as follows:

Germany	11
France	1
Sweden	2
Cuba	1
United States	2
	<hr/>
	17

Dermatomyosites may be defined as an acute, subacute, or chronic disease, of unknown origin, characterized by a gradual onset with vague and indefinite prodromata, followed by œdema, dermatitis, and a multiple muscle inflammation.

Passing over its ætiology, about which there is only conjecture, as well as its morbid anatomy, we will describe its main symptoms, to make our own case more clear.

Symptoms. — The disease generally attacks persons in the

prime of life and in the best of health. The onset is almost always gradual, with the prodromal symptoms of malaise, weakness, anorexia, or headache. Vomiting was seen in two cases. These symptoms may be of several days to three weeks' duration, or even longer, as in one case. Occasionally they are absent.

Pain. — Vague rheumatoid pains are next complained of, as well as a stiffness or rigidity in the extremities and back. These pains quickly take on a more definite character and become localized in the muscles. Different muscle groups are then successively attacked. Eventually the whole skeleton musculature may be involved. Later in the disease the pains are more severe and prevent the slightest movement of the patient being made.

Fever is soon noted, which usually is of moderate intensity, and remittent in character in the later stages of the disease.

Œdema. — With the fever œdema appears which may involve the whole body and extremities, the latter presenting, at times, a most ungainly appearance. It is generally first seen on the face, especially about the eyelids. After the skin inflammation is noted it becomes more intense and may remain localized over the affected muscles or spread to surrounding parts. The wrist and ankle joints are usually spared.

Dermatitis. — A dermatitis is an early symptom and varies greatly in characteristics, being in different cases an erythema, a pseudo-erysipelas, an urticaria, a roseola, or an inflammation resembling erythema nodosum. It may spread continuously or remain limited to the parts where it was first observed. At times its appearance is postponed till later in the disease.

Profuse perspiration and an enlarged spleen usually accompany the other symptoms. The urine is generally normal, but may contain albumen.

The complications, prognosis, diagnosis, and treatment will not concern us now. The history of our case, in brief, is as follows:

John E., aged 31, a laborer and a dark-skinned negro, was admitted to the Johns Hopkins Hospital March 7, 1899, complaining of soreness in his legs, chest and hands, swelling of his muscles and inability to use them.

Family History. — Unimportant.

Previous History. — Negative and unimportant save that he gave a history of having always eaten a great deal of uncooked sausage.

Present Illness. — About six weeks before admission to the hospital he was obliged to stop work because his limbs were sore and swollen. He also suffered from pain in his chest muscles. The onset of his disease began gradually some time before this, but he did not know the exact date. He first noticed the sole of his right foot pained him, especially on walking. It seemed also somewhat swollen. From here the pain and swelling travelled up to the calf of that leg, then into the thigh, and finally to the hip. Soon after this — about one week, he thinks — his left leg was similarly affected. From here the pain and swelling went to his chest muscles.

The patient stayed at home about four weeks, either in bed or sitting up in an easy-chair. At the end of this time he went to work again, but found he could do nothing, for his arms were very sore and weak. Both arms then were affected like the chest and lower extremities. The pain and swelling began in the right hand and went to the forearm and arm, successively. The left arm was next similarly affected. He described the pains as a burning, like the toothache, and said they were mostly present when he moved.

Physical Examination. — Patient was a stout, well-developed man. No puffiness was noted about the eyelids. There was no œdema of the face or body, and no involvement of the muscles of mastication.

Thorax. — The pectoral muscles stood out rather prominently, and seemed swollen. Some pain was complained of on their palpitation. The intercostals were apparently not involved.

The lungs and heart were practically negative on examination. The pulse was 56 to the minute, regular in force and

rhythm, and of good volume and tension. There was slight thickening of the vessel wall.

Abdomen. — Negative. Spleen not palpable.

Extremities. — No œdema noted. Flexion, extension, adduction and abduction slight on account of the pain they caused. The calf muscles were held very much contracted, and seemed to be quite swollen. Patient complained of much pain and tenderness in them, as well as in the muscles of the thighs, forearms and arms. In these latter regions the contractures and swellings were not as prominent, save on the triceps. Palpitation was unsatisfactory on account of the pain it elicited, and consequently a rigid examination could not be made. The muscles apparently were hard and firm. When patient lay quiet and motionless in bed but slight pain was complained of.

Blood Examination. — Red blood corpuscles 5,788,000; white blood corpuscles 5,250; hæmoglobin 70 per cent.

The different count was as follows:

Polymorphonuclears	64.25
Small mononuclears	18.00
Large mononuclears	9.75
And transitionals	1.25
Eosinophiles	6.75
	} 11.00

Shortly after his admission, as the suspicion of his having trichinosis was entertained, a section of his left gastrocnemius muscle was excised under cocaine anæsthesia. The examination of this, teased in salt solution, was negative for trichinæ. "The individual fibres showed quite marked degeneration. They were studded with minute granules which varied slightly in size, and looked like fatty granules; many of the fibres had practically lost their transverse striation." The further examination of this muscle will be elsewhere related.

The electrical examination showed nothing especially worthy of remark.

On April 8 he complained of a feeling as if "something was crawling down from the elbows of each arm to the

fingers." This was especially noted at night. After about eleven days this symptom disappeared, and he seemed to have better use of the muscles of his arms. From then on his strength returned rapidly. He was discharged on May 2 in excellent condition.

Urine, on admission, pale amber in color, clear, 1023 in specific gravity, acid in reaction, negative for sugar, but contained albumen to the amount of 0.15 per cent. There was no apparent sediment. Microscopically a few hyaline and granular casts. The urine gradually cleared up, and, on last examination, made just before patient's discharge, there was only a trace of albumen, and no casts were seen.

Temperature, on admission, 100.2. It was normal the next day, and so continued till March 12, when, without any apparent reason, it rose to 101.8. It was normal again in three days, and so continued till patient's discharge.

His subsequent movements were lost track of about a year, for although he promised to come daily to the dispensary for electrical treatment, yet after one visit he disappeared. He was not known at the address he gave us.

He was admitted again to the Johns Hopkins Hospital on Feb. 10, 1900, complaining of cough, soreness in his arms, and weakness.

Since his discharge from the hospital he had remained quite well until nine weeks previous. The present attack occurred then because he got "overheated on a warm day." Dizziness, with impairment of vision, was the first symptom. It came on suddenly, and obliged him to stop work. During the attack his arms were chiefly involved, and muscular cramps (a late symptom in this disease) were frequently complained of.

In his physical examination the muscles everywhere felt very soft and flabby. There was marked loss of muscular power. The eosinophiles had fallen to five per cent. in the differential count. The urine examination was practically about what we found on his first entrance to the hospital. His temperature varied between normal and 99 degrees. He left the hospital in good condition on March 21.

During his stay a piece of muscle from the left biceps was excised for microscopic examination.

He gave this time, also, the wrong address, and we consequently have been unable to locate him.

Portions of the muscle first removed were hardened in alcohol, bichloride of mercury, and Zenker's fluid. Celloidin and paraffin were used as imbedding agents. The sections were mostly stained with hæmatoxylin and eosin, safranin, congo red, picro-carmin, and Van Gieson's fluid. The Gram-Weigert stain failed to show the presence of bacteria. No animal parasites were found.

In every section some muscle fibres presented a peculiar *anomaly*. As seen on cross section this consisted in a collection of fibrillæ cut transversely and encircled by a longitudinal band of muscle. Instead of one collection of fibrillæ three or more bundles could be so surrounded. The muscle making up this anomaly could be normal in structure, but more frequently signs of degeneration were found, affecting first the centrally placed transverse fibrillæ. These would stain more intensely in eosin, but still reveal the structures that go to make up the Cohnheim fields. In subsequent stages this was difficult or impossible to make out. Finally, an intensely eosin-staining mass was seen presenting the characteristics of waxy degeneration. The surrounding or encircling longitudinal bundles were rarely concerned, but if involved, the degeneration would begin with the innermost fibrillæ, and go from there out to the periphery. These bundles were never attacked until the whole transverse band had undergone waxy degeneration.

In longitudinal sections similar changes were seen. The first stage in the degeneration seemed to consist in the contraction of the inner or now longitudinal fibrillæ by which the cross striations were rendered more prominent. Then cleavage of these fibrillæ would be noted, and a subsequent waxy condition of them, with a loss eventually of their cross striation. The whole anomaly would occasionally show a marked curling or twisting such as is met with in degenerating muscle fibres.

The *sarcolemma* was generally normal, but could show the peculiar blebbing or vesicular condition which Hoen has described in some degenerated voluntary muscle fibres of the uvula. This blebbing was quite a rare find, and its origin and development could not be so well traced as in Hoen's case. It appeared to correspond to his description, except that the granular material in the blebs was only seen in a few instances, and it could not be determined whether this came from the disintegration of the fibrillæ. The more advanced the degeneration the larger the bleb, but no completely destroyed fibre was observed.

The muscle *nuclei* presented at times a normal appearance, but more frequently they were swollen, vesicular in shape, and contained one to two nucleoli with chromatin granules. They were distributed over the whole extent of the fibre, and were often found between individual fibrillæ of fibres which had undergone waxy degeneration. If this degeneration was extreme then these nuclei also showed changes. They would be of no definite shape, swollen or decreased in size, would stain intensely in hæmatoxylin, and assume bizarre positions.

As a rule these muscle anomalies were somewhat below the average size of the muscle fibres; they were round or oval in shape and could be found singly, when they were generally larger in size, or in groups of six or more. They were scattered over all the sections examined and seemed to bear no special relation to the muscle spindles or normal muscle fibres.

The *muscle* not taking part in this anomalous condition showed interesting changes. Many of the degenerations described in muscles could be seen. They could be normal, or swollen and œdematous, or atrophied. First the parenchymatous changes were noted by which the striations failed to come out distinctly in staining. Then the different gradations of waxy degeneration could be made out, and finally a completely homogeneous mass was alone discernible. This was especially to be observed at the cut ends of the fibres and was probably here due to surgical trauma, as Erb and

Weber have pointed out. Occasionally by the tearing of a fibre a gap was observed, due to the retraction of the contractile substance which showed the waxy degeneration. The sarcolemma sheath enclosed this gap, and within were found very fine granules which took the eosin stain. By the lack of simultaneous retraction there could be seen in places irregular cross bands of muscle, also waxy in character. At times this waxy condition had entirely disappeared, and the thickened sarcolemma sheath alone remained filled with rather fine eosin-staining granules.

Longitudinal cleavage was observed here as in the fibres of the muscle anomaly. Cross cleavage was also made out, but rather infrequently. It could not be determined whether the cleavage took place in the membrane of Krause or the plane of Hensen. Fatty degeneration of the muscle was not observed in any of the sections examined.

Vacuolic degeneration was a rare find. In all the muscles so affected a swelling of the fibre was seen, and at times a slight loss of the cross striation. The vacuoles were generally round or oval in shape, of varying sizes, and so situated that their long axes were parallel to the long axes of the fibres. Their edges were sharp and well defined in every case, and their contents consisted of a coarsely or finely granular material containing occasionally two or three nuclei. The vacuoles at times were present in such numbers that the fibre on cross section appeared riddled with them. As Schaefer has described, their appearance seemed to be heralded by a round, or oval, opaque, non-staining area in a muscle fibre.

In one place there was a considerable extravasation of blood between the fibres.

The *sarcolemma sheath* showed the vesicular degeneration, as above described, rather infrequently. Occasionally the sheath was considerably thickened, especially if its muscle had been completely destroyed.

The *nuclei* in an unchanged fibre were normal, but with commencing degeneration they would greatly increase in number and occupy the centre as well as the periphery of

the fibre. By still further increasing in number they could almost hide the structure of the muscle. They were oval or vesicular in shape, and contained one to two nucleoli. Their long axes were, as a rule, parallel to the long axes of the fibres. At times they would undergo degeneration, become shrivelled up, stain densely, and lie with their long axes at right angles to the long axes of the fibres. They disappeared apparently by karyolysis. In no place where there was this proliferation of nuclei would new muscle fibres be found, but occasionally what might be called reparative processes were observed. The nuclei would lengthen out and become like a rod. Then two or three nucleoli would be seen in them, and indentations indicating a commencing division. Finally one of these rods would form fourteen or more nuclei. The next step was the taking on of protoplasm by these nuclei and their formation into myo- or sarcoblasts. They received this protoplasm at the expense of the contractile substance of the muscle fibre, and consequently might lie in hollows of the fibre, or, exhausting the whole contractile substance, might simply be enclosed by the sarcolemma sheath. Up to this point amitosis was alone observed, but now the myoblasts can show exquisite examples of karyokinesis. These myoblastic cells at times exhibited degenerative processes. Their nuclei would then stain deeply and finally disappear, leaving the cell protoplasm, which would take on an intense eosin stain. By the total destruction of all these cells the sarcolemma sheath might be so pressed together as to make it difficult to recognize.

Muscle regeneration by the longitudinal cleavage of old fibres and the subsequent budding of the same was also not observed, though longitudinal cleavage of a collection of fibrillæ from an old fibre was occasionally met with.

Muscle Spindles were at times noticed in the sections, but there was no increase in their frequency or any pathological change discernible.

Nerves. — The nerves seemed normal in structure, save that in some instances there was an increased number of nuclei in the sheath of Schwann.

Connective Tissue. — The increase in small round cells in the perimysium externum and internum was comparatively infrequent. It could be seen, especially in the perivascular connective tissue space of the former. Much more marked in these situations was the increase in connective tissue, which was more noticeable in the perimysium externum. The tissue was oedematous and very loose in structure. Occasionally it was seen taking the place of a completely degenerated muscle fibre or a collection of fibres. It was especially rich in newly formed blood-vessels. The increase in fat cells was quite marked. In places the connective tissue showed a waxy or granular change, and an eosin-staining granular mass might alone remain. Large multinucleated giant cells were sometimes seen in the connective tissue, near degenerated muscle fibres.

The muscle excised from patient's left biceps, on his second admission, was hardened in alcohol, imbedded in celloidin, and the sections were stained in hæmatoxylin and eosin. The muscle anomaly above described was wanting in all these sections examined, but a distinct myositis was present, which chiefly consisted in a great increase of connective tissue between the fibres.

It seems fair to conclude that the above case was one of dermatomyositis, though it is unfortunate that in the light of our further knowledge we have been unable to question the patient more minutely on some of the symptoms in this disease. The swelling spoken of at onset was probably oedema, which is always associated with dermatomyositis. No oedema, however, was noted on patient's admission to the hospital. He was not asked as to a skin eruption, but if it consisted of merely an erythema he might easily overlook it on account of his color. Microscopically the findings are identical with those seen in this affection.

I have been unable to find a satisfactory explanation for the muscle anomaly. It has been described in two instances and two explanations have been given for its occurrence. Both, however, seem unlikely and somewhat fanciful. Bataillon found it in the frog larva. He claims it is a degenerative

process and says it begins by the tearing of certain of the outermost fibrillæ of a muscle fibre. These torn fibrillæ then circumscribe those centrally located and are more or less obliquely placed. They run in all directions and are plainly separated from the central bundle. Often they show a more regular arrangement and, by cross section, may be seen to encircle as a ring, with longitudinal fibrillæ, the transversely cut fibre. The regularity of the cross and radial striations speaks strongly against this view.

J. Schaffer, on the other hand, thinks the muscle is not at all here concerned. The encircling ring or band is due, he claims, to the sarcolemma which by a peculiar arrangement simulates muscle striations. It is generally found on atrophied fibres whose sarcolemma sheath has ruptured. After the rupture the sheath is retracted and drawn down in folds over the muscle, below the site of rupture. The fibre above the retraction is consequently without its sheath and its fibrillæ are here widely spread apart. The successive infoldings of a retracted sarcolemma sheath then cause the appearance of the circular striations. Our sections refute this theory, as the outer ring or band of fibrillæ can be plainly seen, shrunk away from the encircling sarcolemma sheath. The radial striations may possibly be due, he says, to the acids used in Fleming's solution — the hardening agent employed. Some of the tissue was hardened in Müller's fluid, and similar pictures were seen, due, as Schaffer conjectures, to a contraction caused by the imbedding process. The muscle in this case was from the gastrocnemius of a healthy man.

In the lower types of vertebrates and invertebrates a bundle of transversely cut fibrillæ is found in cross sections of muscle surrounded by a band of longitudinal fibre, which is in turn encircled by sarcolemma with a layer of undifferentiated sarcoplasm. Kölliker, Roelet and others have described such pictures. Our anomaly, consequently, may be looked upon as a structure reverting to that seen in lower types. Atavism, however, would not explain, but merely place the question in another phase.

In the other instance found in man it was also seen in the gastrocnemius muscle, so it might be a normal structure of that muscle and have some hitherto unknown function. It is our purpose to study further the histological structure of human gastrocnemii muscles to see how frequently the so-called anomaly occurs and if it has any functions of its own. It is interesting to note it was not found in Kell's case of dermatomyositis, though the gastrocnemius was examined.

I am indebted to a number who have looked over my sections and given helpful suggestions; especially do I desire to thank Dr. William H. Welch for his kindly aid and valuable advice, and Dr. William Osler for allowing me to report this case.

THE EFFECT OF CARBON DIOXIDE AND OXYGEN ON SMOOTH MUSCLE.¹

ALLEN CLEGHORN, ASSISTED BY H. D. LLOYD.

(From the Laboratory of Physiology in the Harvard Medical School.)

A ring of smooth muscle, made by two parallel sections across the stomach of the frog, including the mucous membrane, was suspended from a metal electrode in a moist gas chamber; a second electrode attached the muscle to a lever writing on the smoked surface of a Baltzar drum. The electrical stimulus used was the make and break shocks of a constant current furnished by two Daniell cells connected in series. CO_2 and O_2 were passed into the muscle chamber at will, both gases first passing through wash bottles. These gases were run into the chamber both while the muscle was contracting spontaneously and when it remained quiescent, but reacted to the electrical stimuli.

The results obtained were compared with the contractions (spontaneous and stimulated) of the muscle when in ordinary air.

In order to guard against errors from local polarization at the metal electrodes the experiments were repeated with non-polarizable electrodes. The same results were obtained.

The following results were obtained:

1. On passing carbon dioxide through the gas chamber an almost immediate increase in the tonus of the muscle took place.
2. When this increase in the tonus was great electrical make currents had no effect, but break currents often caused a fall.
3. While the muscle was contracting spontaneously carbon dioxide caused a rise in tonus, but eventually stopped the contractions.
4. Electrical stimulation while the muscle was under the

¹ To be published in full in the American Journal of Physiology, vol. v, 1901.

influence of carbon dioxide was followed by a long and slow contraction.

5. Oxygen gave no pronounced effect during spontaneous or stimulated contraction. Sometimes the spontaneous contractions appeared larger but less frequent.

6. Often the break current caused a larger contraction than the make; carbon dioxide would then reverse the result.

7. Carbon dioxide prolonged the latent period considerably.

8. When spontaneous contractions of the muscle were brought to a standstill by carbon dioxide, recovery did not seem to be accelerated by the application of oxygen.

[Abstracts of papers presented at the Second Annual Meeting of the American Society of Bacteriologists, Baltimore, Md., December, 1900. Received from the Secretary.]

DISTRIBUTION OF BACILLUS AEROGENES CAPSULATUS.
(BACILLUS WELCHI, MIGULA.)

WILLIAM H. WELCH.

Dr. William H. Welch presented the results of investigations of Mr. Leonard K. Hirshberg in the Pathological Laboratory of the Johns Hopkins University.

There can be no question but that the bacillus discovered by Welch in 1891, and fully described by Welch and Nuttall in the following year, is identical with Fraenkel's *B. phlegmones emphysematosae*, with Veillon and Zuber's *B. perfringens*, and with Schattenfroh and Grassberger's *Granulobacillus sacchar butyricus immobiles liquefaciens* described in 1900. It is possible that Klein had in his cultures *B. aerogenes capsulatus*, but his description of his *B. enteritidis sporogenes* cannot be reconciled with the properties of the former bacillus, especially his statements as to motility and peptonization of milk.

It has already been demonstrated by Welch, by Howard, and by Hitschmann and Lindenthal that *B. aerogenes capsulatus* is a widely distributed organism, its natural habitats being especially the intestinal canals of man and other animals, and the soil. Mr. Hirshberg has, during the past summer, made a systematic study of the distribution of this bacillus in various situations. Various methods were employed for its isolation, one of the most useful being the inoculation into the circulation of rabbits, which were then killed according to the procedure described by Welch and Nuttall. In each instance the bacillus, if found, was isolated in pure culture, and identified by its characteristic properties.

B. aerogenes capsulatus was found by Mr. Hirshberg regularly in the feces of man (being isolated from all parts of the intestinal canal), of swine, of dogs and of cats, and

was found with varying frequency, as a rule, in 50 to 80 per cent. of the animals examined, in the feces of rabbits, guinea-pigs, mice, rats, chickens, pigeons, and cows. It was likewise obtained from the excrement of flies hovering around the bodies of infected animals or human cadavers. It was isolated constantly from garden earth, rarely from street dust. It was detected four times out of eighteen in examinations of dust swept from the floors of hospital wards, the dispensary, or the laboratory. Once it was obtained in scrapings from the human skin. It was isolated twice from cesspools. The results of Schattenfroh and Grassberger concerning the presence of this bacillus in market milk were confirmed.

In the light of these and previous investigations *Bacillus aerogenes capsulatus* must be regarded as one of the most widely distributed of bacteria.

THE BACTERIAL CONDITION OF CITY MILK AND THE NEED
OF HEALTH AUTHORITIES TO PREVENT THE SALE OF
MILK CONTAINING EXCESSIVE NUMBERS OF BACTERIA.

W. H. PARK.

The author raised the question whether it is possible for Health Boards to set a limit to the number of bacteria which milk may contain, and above which its sale could be prohibited.

During the coldest weather the milk in New York City averages about 250,000 bacteria per cc., during cool weather about 2,000,000, and during hot weather about 5,000,000. The milk in other large cities is, from all accounts, in about the same condition.

The above statement does not apply to the special milks, which contain only from 5,000 to 20,000 bacteria at the different seasons of the year.

In answer to the question whether these enormous numbers of bacteria found in milk during the hot weather are harmful, reference need only be made to the universal clinical experience that a great number of children in cities

sicken on the milk supplied in summer; that those who are put on milk that is sterile, or contain few bacteria, as a rule mend rapidly; while those kept on the impure milk continue ill, or die.

We probably have, as yet, insufficient knowledge to state just how many bacteria must accumulate to make them noticeably dangerous in milk, but it is a safe conclusion that no more bacteria should be allowed than it is practicable to avoid. Any intelligent farmer can use sufficient cleanliness and apply sufficient cold, with almost no increase in expense, to supply milk twenty-four to thirty-six hours old which will not contain in each cc. over 100,000 bacteria, and no milk poorer than this should be sold.

The most deleterious changes which occur in milk during its transportation are now known to be due to the changes produced by bacterial growth and activity. These add to the milk acids and distinctly poisonous bacterial toxins to such an extent that much of the milk, by the time it is used in summer, has become decidedly injurious to invalids and infants. While it is the universal custom for health authorities to guard the quality of their milk in many ways, they nevertheless entirely fail to prevent the sale of milk rendered unfit for use through excessive numbers of bacteria and their products. This seems all the more remarkable when we consider how comparatively easy the test and how rapidly the farmer and middleman could greatly improve the bacterial purity of their milk if only their dense ignorance and lack of desire to improve could be removed.

A. DURATION OF LIFE OF TYPHOID BACILLI, DERIVED FROM TWENTY DIFFERENT SOURCES, IN ICE. — *B.* EFFECT OF INTENSE COLD ON BACTERIA.

W. H. PARK.

a. Cultures derived from twenty different cases of typhoid fever were grown twenty-eight hours in nutrient agar. From each one a loopful was inoculated into 300 cc. of sterile dis-

tilled water and this poured into thirty glass tubes. These were kept in a room averaging 23° F. (—5° C.). From time to time a tube from each lot was removed and the number of bacilli which should develop in nutrient agar tested.

The following table gives the results :

Number of weeks frozen.	Per cent. of bacilli living.	Per cent. of cultures living.
0 (Original)	100	20
1½ week.....	42	20
1 “	14	20
2 weeks.....	7.50	20
3 “4	20
5 “11	18
7 “09	18
9 “05	17
12 “005	11
15 “002	8
18 “0001	3
22 “	None.	0

b. Watery suspensions of typhoid, colon diphtheria, and hay bacilli, and of the Staphylococcus pyogenes aureus were placed in small tubes, and dropped into liquid air. From time to time the tubes were removed, and the contents plated in nutrient agar. The percentage living was as follows :

Per cent. living after exposure of	Typhoid.	Colon.	Staph.	B. subtilis.
3 minutes.....	18	19		
20 "	10	11	85	80
60 "	7.5	8	51	67
130 "	3	5.5	27	55

The virulence of the organisms was only slightly diminished by this intense cold for two hours.

THE USE OF PARAFFIN TO EXCLUDE OXYGEN IN GROWING ANAEROBIC BACTERIA.

W. H. PARK.

Nutrient glucose bouillon in tubes or flasks covered with a layer of paraffin melting at 42° C. has proved very useful in the development of tetanus cultures and toxins, and of other anaerobic bacteria. With bacteria not possessing spores the media is quickly cooled and inoculated, and then covered by a layer of very hot sterile paraffin. The accumulation of gas forces the paraffin up in the tube or flask, but does not allow the entrance of oxygen. When absolute exclusion of oxygen is desired the tubes with their layer of paraffin are sterilized in an autoclave which renders them free from oxygen. Spore-bearing bacteria are inoculated through the liquid paraffin before the bouillon is fully cooled. Bacteria without spores are inoculated by breaking through the paraffin film or by heating the paraffin in a gas flame. A pipette can then be carried through the hot paraffin into the cool liquid below. The paraffin layer has also been found useful in preserving media from drying or from changes due to the absorption of gases of the air.

THE EFFECT OF SALT SOLUTION AND OTHER FLUIDS ON
BACTERIA COMPARED WITH SERUM REACTION.

ADOLPH GEHRMANN.

The author described, first, a series of experiments to determine the effect upon bacteria (typhoid and colon bacillus) of transferring them from one solution to another in which the percentage of salt is less. These experiments showed that, if the salt was not stronger than one per cent., the solution did not materially injure the bacteria, and did not produce the plasmolysis and plasmotypsis described by Fisher. Solutions of one per cent. have an inhibiting action, and cause typhoid cultures to develop long chains, and to lose their motility.

A second series of experiments tested the effect of salt in the diluting fluids which were used in making the serum tests. Distilled water, normal salt solution, and a bouillon culture fluid, made both with .5 per cent. salt and without salt, were compared side by side, and were found to be fully equivalent. Blood diluted with any of the above readily produced the agglutination test, about the same time elapsing in all cases before the agglutination occurred.

A further series of experiments tested the influence of the viscosity of fluids upon motile bacteria, as aiding in explaining agglutination. These experiments showed that the typhoid bacillus becomes readily agglutinated in fluids having considerable viscosity.

For testing this phenomenon, gelatine and egg albumen were used, both of which caused the bacilli to adhere in clumps, which, however, were dissipated if the solutions were diluted.

While these observations were regarded as having significance in interpreting the serum test, the author was of the opinion that, when properly conducted, the agglutination obtained in the serum test can readily be distinguished from that which is the result of such physical conditions.

GROWTH OF BACTERIA IN THE PRESENCE OF CHLOROFORM
AND THYMOL.

ERWIN F. SMITH, Washington, D.C.

As an illustration of the frequent dependence of bacteriologists and physiological chemists upon chloroform as an antiseptic, the speaker cited various passages from the recent valuable English work of Green on "The Soluble Ferments and Fermentation." In this book there are many statements and implications that animal and vegetable infusions can be preserved from bacterial growths during their examination by the addition of chloroform. Twelve micro-organisms are known which grow readily in test-tube cultures of milk, beef bouillon, etc., to which an equal volume of chloroform has been added. This probably by no means exhausts the list. Test-tube cultures of eight of these organisms growing readily in presence of chloroform were exhibited. Two organisms are also known which grow readily in beef bouillon to which thymol has been added. It would appear, therefore, that there is no general rule, but that each bacterial organism must be tested by itself as to the effect upon it of chloroform, thymol, etc.

If chloroform is used to preserve fluids or macerations of animal and vegetable substances from the growth of micro-organisms, it would be well to seal the flasks and to keep them constantly agitated. Moreover, if one would be certain of their continued sterility, the freedom from bacterial growth of the substances under examination must be determined from time to time by microscopic examination and by cultures made from the fluids or macerations; otherwise, especially where bacterial organisms are able to produce the same substances as those sought for in plant or animal tissue, *e.g.*, cytase, diastase, etc., there can be no certainty as to the exact origin of the substance in question.

INFECTION BY MEANS OF MODELLING-CLAY.

M. O. LEIGHTON, Montclair, N.J.

The author's attention is drawn to the possibility of the distribution of infectious disease among school children by the common use of modelling-clay. In the ordinary schools such clay, after having been used by one student, is returned to the stock box and subsequently used again. Study of such clay obtained from schools showed bacteria to be tolerably abundant in it. The species of bacteria identified were those which ordinarily occur in pus formations, thus showing that clay may be capable of distributing these organisms. An attempt to sterilize clay showed that the only efficient means of accomplishing this purpose is by the use of super-heated steam under a pressure of 15 to 20 pounds for 45 minutes. Next, an attempt was made to determine how long certain pathogenic bacteria could remain alive in the clay. Sterilized clay was inoculated, under proper precautions, with the bacilli of typhoid, diphtheria, and tuberculosis. The clay was then kept moist and warm and studied periodically for the presence of these organisms. The results were, briefly, as follows: *B. typhi abdominalis* grew vigorously after having been enclosed in the clay for thirty-two days. After that no colonies were found. *B. diphtheriæ* grew after having been enclosed in the clay for eighteen days. *B. tuberculosis* was alive after eighteen days. How much longer the two latter bacilli would remain alive in the clay the author did not determine. The experiments, however, sufficiently demonstrate that the indiscriminate use of modelling clay in the schools is unwise, and liable to distribute communicable diseases, if such are present among the pupils.

A PRELIMINARY REPORT UPON A HITHERTO UNDESCRIBED
PATHOGENIC ANAËROBIC BACILLUS.

NORMAN HARRIS, Baltimore, Md.

This organism was isolated, post mortem, from one of several abscesses in the liver of a man who had entered the

service of Professor Halsted in the Johns Hopkins Hospital of Baltimore. He complained of great pain in the hepatic region of the abdomen, accompanied by nausea, vomiting, and jaundice. Blood examination showed a marked leucocytosis. Exploratory laparotomy was performed, and the condition was found to be one of multiple abscess of the liver, and beyond radical treatment. The patient died upon the fourth day after operation.

The autopsy disclosed the presence of numerous abscesses throughout the liver, as well as in the right lung and spleen.

Petri dish cultures were made in plain and in hydrocele fluid agar, and grown both aërobically and in an atmosphere of hydrogen for a period of seventy-two hours. All dishes showed no growth, excepting the undiluted hydrocele fluid culture which had been in the hydrogen atmosphere. This developed four colonies surrounded by a halo of growth, and these appeared to arise from small particles of liver detritus. Sub-cultures were successfully grown only when the media were made up with hydrocele fluid or human blood, and oxygen excluded.

Characteristics: The organism is a bacillus which in general is not minute, although its size varies somewhat on the various media. It may occur as cocci, diplococci, very short rods, longer rods, filaments, or more rarely as chains of cocci or very short rods. Occasionally some rods are seen to have swollen ends, or may show distinct polar granules, or may be slightly curved.

It is non-motile; it is decolorized by Gram's method of staining; it does not liquefy gelatin; it does not appear to have spores; its thermal death point is an exposure of ten minutes at 50° C.

In all media it gives off a very strong fecal odor, and forms gas from ordinary and sugar-free beef broth, when made up with either hydrocele fluid or blood; it likewise actively ferments glucose, forming CO₂, H₂, and H₂ S, the gas igniting readily.

Experimentally, lesions similar to those found in the human subject were reproduced in rabbits and guinea-pigs, and mice

succumbed to subcutaneous inoculation with a local necrotic lesion only.

The name proposed for the organism is *Bacillus mortiferus* or *Bacterium mortifer*.

The organism differs essentially from any of the anaërobic bacilli hitherto described.

CONCERNING THE THEORIES OF SILAGE FORMATION.

H. L. RUSSELL AND S. M. BABCOCK, Madison, Wis.

The authors instituted a long series of experiments to determine whether the changes that take place in the silo are due to micro-organisms, as has been believed, or to other kinds of action. Their conclusions are: (1) Silage can be made under conditions that exclude bacterial activity. (2) The initial heating of the silage is due, mainly, to the respiratory processes of the cut plant tissues. (3) The peculiar characteristic of good silage is due, not to bacteria, but to changes inaugurated under the more or less direct control of the activity of the protoplasm of the plant tissues. The acids of silage seem to be for the most part a product of the intramolecular respiration, and in quantity are roughly proportional to the length of time that ensues before the cells stop respiring. This fact explains the reason that silage from immature corn has a higher acidity, and is more likely to undergo putrefactive changes due to bacteria growing in the succulent tissues than silage made from mature corn. (4) The aroma of good silage can be produced under conditions in which all vital processes are suspended. This seems to point strongly to the idea that enzymes are operative in the production of this aroma. It has previously been shown that such ferment bodies are liberated from dying vegetable cells, and that they continue to act after the cells lose their vitality.

DEMONSTRATION OF SOME NEW LABORATORY DEVICES.

F. P. GORHAM, Providence, R.I.

The following laboratory devices were demonstrated:

1. The application of the incandescent electric lamp to heating incubators, water and paraffin baths.
2. Culture tubes with etched surface for writing data.
3. Large slides for the examination of series of cultures.
4. Cotton "sliver" for plugging tubes, etc.

(See this Journal, Vol. IV., p. 270.)

A LOW TEMPERATURE INCUBATOR.

E. H. WILSON, Brooklyn, N. Y.

(Read by title.)

A. — PRESERVATION OF SPUTUM FOR MICROSCOPIC
EXAMINATION.

B. — A NEW FERMENTATION TUBE.

C. — SIMPLE DEVICE FOR DISTRIBUTING EQUAL QUANTITIES
OF CULTURE MEDIA.

A. ROBIN, Newark, Del.

A. — Preservation of Sputum for Microscopic Examination. The author has experimented with some of the active germicides with a view to preserving tuberculous sputum. Carbolic acid 5 per cent. solution, trikresol 2 per cent., formaldehyde 5 per cent., and hydrochloric acid 10 per cent., were added to sputum containing large numbers of tubercle bacilli. The coagulation resulting from the addition of carbolic acid or trikresol to sputum containing pus was largely overcome by vigorous shaking, the coagulation being thus finely broken up. The sputum was examined at the end of twenty-four to forty-eight hours. Weekly and then monthly examinations were made for a period of four months. Except when hydrochloric acid was used, the bacilli were found well preserved and, if anything, stained much more deeply. HCL, on the other hand, seemed to have either so

disorganized the bacilli or so changed their staining properties that they could not be found at the end of twenty-four hours. As a result of these experiments the author recommends the addition of an equal volume of a 5 per cent. solution of carbolic acid to the sputum, which should be vigorously shaken up in the bottle so as to break up the lumpy coagulation.

B. — A New Fermentation Tube. The apparatus is illustrated by the accompanying drawing. (Plate XXXIII.) The side tube *c* is packed with non-absorbent cotton, the arm *A* of the U tube is filled with mercury, the tube *B* is filled with the culture, when the rubber stopper holding the side tube *c* and straight tube *d* is tightly inserted. When this is done the end of *d*, which serves for the escape of air displaced by the stopper, is sealed in the flame. The gas generated in *B* escapes into the closed arm *A*, displacing the mercury. To determine the CO_2 ratio, the tube *B* is filled to the rubber stopper. Two fermentation tubes are used. In one, the arm *A* is filled with mercury; in the other half the arm is filled with a saturated solution of sodium or potassium hydrate, this being readily accomplished by inclining the U tube towards the operator. The CO_2 passing through the caustic solution is absorbed, and the unabsorbed gas (*H*) is left. The ratio between the two is then determined.

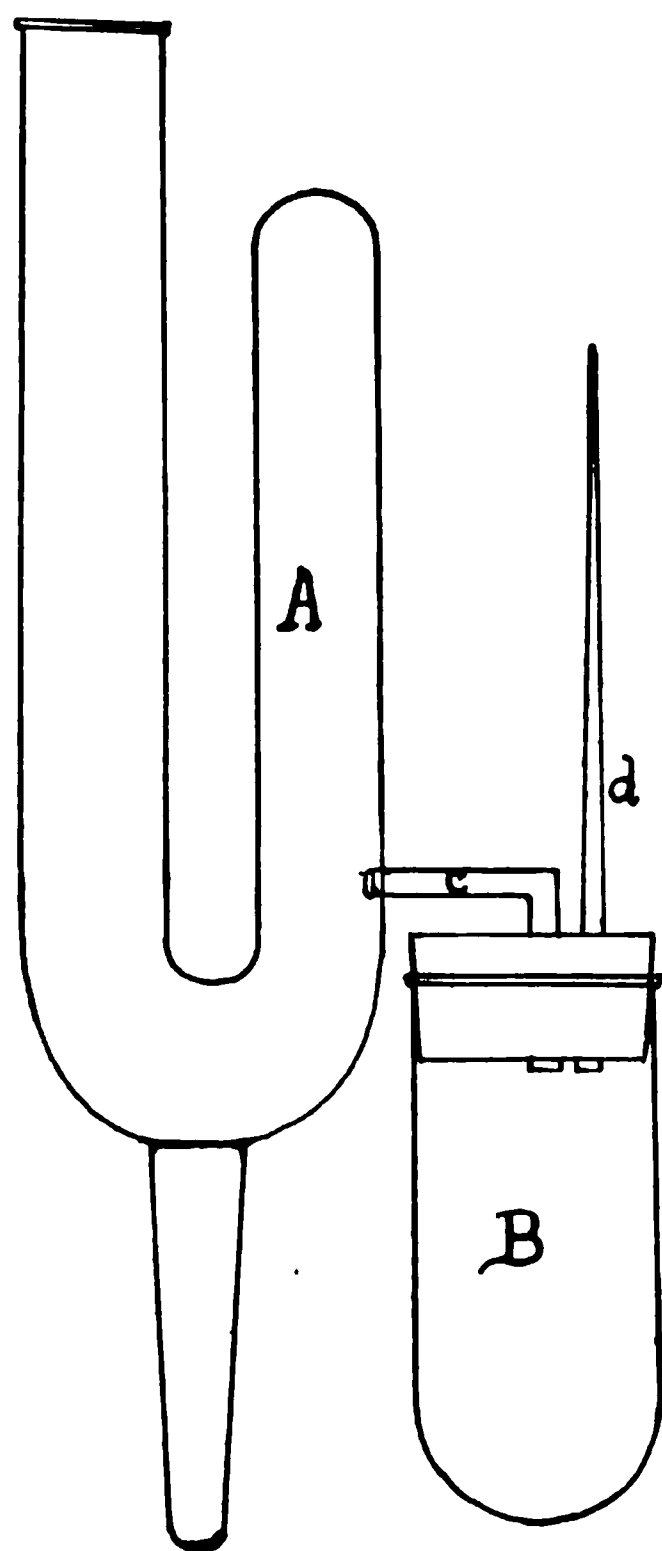
C. — Simple Device for Distributing Equal Quantities of Culture Media is illustrated in Fig. 2,¹ which is self-explanatory. The end of the rubber tubing *a* is connected with a funnel into which the culture medium is poured.

A NEW METHOD OF APPLYING THE RABIES TEST.

CHAS. F. DAWSON, Detroit, Mich.

The author, in his work upon rabies, was dissatisfied with the current method of inoculating animals in the cerebrum,

¹ Figure not sent. — EDITOR.



ROBIN.

FERMENTATION TUBE.

which involved trephining the animals, with occasional death from hæmorrhage, possibility of self-inoculation, and other difficulties. He has, therefore, devised a method of inoculation in which these objections are reduced or eliminated. The method is as follows: A bit of the brain of the suspected animal is ground in a mortar containing sterilized 6 per cent. sodium solution, and is then filtered through sterilized cotton. Two minims of this solution are then injected on the base of the anterior cerebrum by way of the optic foramen. To accomplish this, full-grown rabbits are used, which are thoroughly anesthetized with ether. A hypodermic syringe is used with a needle seven-eighths of an inch long. The inoculation is made by lifting the nictitating membrane out of the way by means of the syringe needle, and then forcing the needle upwards and backwards through the orbital tissues until it enters the optic foramen. The contents of the syringe barrel are then injected and the needle carefully withdrawn. By this means the solution is injected underneath the cerebrum and the chances of injury to the animal are much lessened. In a series of comparative tests made with this and the ordinary method, the author reaches the conclusion that the new method is fully as satisfactory as the old and much easier to apply.

THE USE OF CARBOLIC ACID IN ISOLATING THE BACILLUS COLI COMMUNIS FROM RIVER WATER.

WILLIAM R. COPELAND, Pittsburg, Pa.

The author described a method which he had devised for the purpose of separating the colon bacillus in river water, by the use of solid media. For this purpose he used Wurtz's agar, inasmuch as it could be incubated at 37° and the acid colonies were readily distinguishable by the reddening of the litmus. Inasmuch, however, as many other bacteria were present in river water, especially after a rain, which can develop at 37° C., it is quite desirable to devise some means by which they may be reduced without affecting the colon bacillus. The author accomplishes this by add-

ing to the agar two-tenths cc. of a two per cent. solution of carbolic acid. Experiments showed that such addition of carbolic acid reduced the total number of bacteria about 45 per cent., while it had no effect, apparently, upon the colon bacillus. This makes it possible to determine the number of colon bacilli in water much more readily than if all bacteria are allowed to grow. By the use of this method, a study of the relation of the muddiness of river water and the number of colon bacilli was made. The result showed that, leaving out certain irregularities due to abnormal conditions, the number of colon bacilli increased with the turbidity of the water, a relationship pointing to an increase in sewerage pollution at times when the water of the river becomes turbid. The author recommends the use of carbolic acid as described in the employment of solid culture media for the determination of the number of colon bacilli present in surface waters without dilution.

A FEW EXPERIMENTAL DATA ON HYPODERMIC INJECTIONS.

S. J. MELTZER, New York City.

From two series of experiments Meltzer arrived at the conclusions:

1. That the effect of a subcutaneous injection depends to a very large degree upon the concentration of the injected fluid and very little, if any, upon its bulk.

2. That the effect is distinctly increased by a distribution of the injected quantity over several areas.

The author employed crystalloid solutions and restricts his conclusions to this kind of liquids.

THE UTILITY OF A SUPPLY OF LIVE STEAM IN THE LABORATORY.

H. A. HARDING, Geneva, N.Y.

The expense connected with cooking and sterilizing in the bacteriological laboratory is usually great, because of the high cost and low efficiency of gas. As a saving of time and

money, the advantage of using steam generated directly by coal is obvious.

In fitting up the Bacteriological Laboratory at the New York Agricultural Experiment Station, the following devices have been tried and found satisfactory.

In the case of the Arnold sterilizer, a steam pipe was introduced through the wall of the passage in which the steam normally rises into the sterilizing chamber, and an elbow screwed to the end of this pipe and turned downward. With this connection the Arnold can be brought to a temperature of 99° C. within five minutes, without any unpleasant noise or undue waste of steam.

An autoclave was constructed, differing from the ordinary type in that steam was introduced from a high pressure boiler. By means of a reducing valve the steam pressure and, consequently, the temperature within the autoclave, can be held within very narrow limits. A ten-minute exposure at 120° C. suffices to render tubes of gelatin and other media sterile.

Steam cups were installed having the shape of an ordinary water-bath, except that their depth was considerably increased. A steam inlet was placed at the bottom, and a waste pipe provided for carrying off the condensation. In these cups water is heated and agar is melted much more quickly than it could be done over an ordinary Bunsen burner, and in cooking media there is no possibility of boiling over or burning.

The above pieces of apparatus, together with the hot air sterilizer, are placed upon an eight foot bench and nearly all of the heat radiated is carried off by a galvanized iron hood.

These devices have been in use for nearly two years, and are giving good satisfaction.

BACTERIA IN THE AMES SEWAGE DISPOSAL PLANT.

L. H. PAMMEL, Ames, Iowa.

The author describes a sewage plant designed for the disposal of the sewage of about six hundred people. The

plant is of the ordinary type, consisting of two beds, each covering about one-fifth of an acre. The filtration in the beds was at the rate of about 100 gallons a day, per acre. The whole plant was installed for about \$3,000. The efficacy of the filter bed was shown by bacteriological analysis. The effluent of the filter bed for 1899 showed an average of 5,127 bacteria per cubic centimetre, and at no time did it rise over 11,075 per cc.

The number of bacteria in the water in the tank varied largely with the temperature, rising in September to 9,000,000, and falling in colder weather to a little over a hundred thousand in March. The filter bed was, therefore, extremely efficient in removing bacteria.

In the study of the species of bacteria found in the effluent some of the common sewage types were found. The author found, also, in this effluent, *Bacillus prodigiosus*. This was interesting, inasmuch as it made its appearance in the sewage after it had been introduced into the laboratory in Ames. It was not believed, however, to be a native of the locality, but an introduced species.

VARIATIONS OF *BACILLUS ROSACEUS METALLOIDES* (DOWDESWELL).

NELSON G. DAVIS, Lewisburg, Pa.

During the summer of 1896 a series of experiments was begun on the variations of *Bacillus rosaceus metalloides*.

In making a pure culture of the organism, I noticed that one colony was much paler in color than the others. No pigment appeared until the colony was some days old. Replating from this colony, all the daughter colonies were colorless until the fourth day, when a pale pink pigment appeared. After a time the characteristic metallic lustre became visible. A continuation of the replating and selection of colonies was kept up for nine months. By that time there were obtained cultures of the *bacillus rosaceus* varying in color from colorless to a deep red, deeper than the original variety. The darkest variety of all appeared as a "sport;"

so did also the first pale colony. The other variations appeared as gradual modifications.

An attempt was made to produce a variety that would not liquefy gelatine. This was unsuccessful, although in two instances colonies were obtained, much slower than usual in this action.

Similar selection experiments demonstrated great variation in the size of the organism. After about two hundred replatings, there appeared in one of the gelatine plates a colony in which the length of the elements was the same as the breadth. In other words, it appeared to be a coccus 0.5μ . in diameter, and was so described by students.

This variety was cultivated in various media, at various temperatures, in light and darkness. It remained constant in size.

SOME VARIETIES OF BACILLUS PYOCYANEUS FOUND IN THE THROAT.

F. P. GORHAM, Providence, R.I.

Bacillus pyocyaneus is a comparatively frequent form in the nose and throat. Two varieties can be distinguished, one producing both pyocyanin and a fluorescent pigment, the other producing only pyocyanin. These forms are often present in almost pure culture, and may persist in the same individual for several months. The cultures are virulent for guinea-pigs and rabbits.

DEMONSTRATION OF PHOTOGENIC BACTERIA.

F. P. GORHAM.

Cultures of several varieties of phosphorescent bacteria were exhibited at the evening session. They were growing on fish, fish-agar, and fish-bouillon. Some of the cultures were remarkably luminous.

BACILLUS LACTIS VISCOSUS; A CAUSE OF ROPINESS IN MILK
AND CREAM.

ARCHIBALD R. WARD, Ithaca, N.Y.

The writer has closely observed the occurrence of the milk fault known as "ropy milk" in the creameries of three different milk dealers in widely separated localities in New York State. *Bacillus lactis viscosus* (Adametz) has been found to be the cause of trouble in each outbreak. The identification of the organism found in the ropy milk was confirmed by Dr. Adametz, who studied a culture sent for identification, and pronounced it identical with the one first described by himself. Attention is called to the fact that in several textbooks there occurs an erroneous statement to the effect that the organism brings about the viscid condition in milk very slowly, and that it is, therefore, of no practical importance to dairymen. The statement is founded upon a misconception placed upon a sentence written by Dr. Adametz.

The organism is found in water, and multiplies at a temperature as low as (8) eight degrees Centigrade. These characteristics, together with the method of keeping the milk, account for the persistence with which ropy milk appears on a milk route when the creamery is once infected. In all the cases coming under my observation, the milk dealer has cooled the milk in long, open-topped cans standing in ice water. In each case the ice water was found to contain the organisms. These might readily be introduced into the milk by the spattering of water incident to the removal of cans, addition of ice, etc.

That the ice water was the immediate source of trouble was indicated by an experiment in which potassium bichromate was added to the ice water in the proportion of one part to one thousand parts of water. The trouble did not recur in those cans of milk which were placed in the water after the addition of the disinfectant. In this case scrupulous care was observed in sterilizing vessels which had been infected.

CONCERNING THE PRESENCE OF STREPTOCOCCI IN THE
HEALTHY UDDER OF A COW.

R. C. REED AND A. R. WARD.

At intervals between November, 1897, and July, 1900, the presence of streptococci in the freshly drawn milk of a cow in the Cornell University herd was noted. While some cases of mammitis, associated with streptococci, were known to have occurred in the herd during this period, yet we had no record that this cow ever suffered an attack. The fact that she led the herd in butter production during the period in which the streptococci were observed in the milk, indicates that the cow was not suffering from a chronic form of the disease. This fact is significant in view of the serious effect of mammitis on the secretion of milk.

The slaughter of the animal in the summer of 1900 afforded an opportunity to study the bacterial flora of the udder by means of cultures made directly from all parts of the gland. In addition to some organisms commonly found in the udder, streptococci appeared in all of the thirty-six cultures.

In conjunction with the streptococcus under consideration one culture from a sporadic case of mammitis and one from an epizootic of the same disease were studied. In their cultural, morphological, and pathogenic properties the streptococcus from this healthy udder was indistinguishable from those isolated from the cases of mammitis. None were pathogenic to guinea-pigs or rabbits, but all three induced mammitis when injected into a healthy udder.

While these observations are incomplete, they cannot but suggest the idea that the streptococci associated with mammitis may, like the specific organisms of diphtheria and pneumonia in the healthy throat, be harbored in the healthy udder without producing disease.

IMMUNIZATION OF ANIMALS TO RATTLE-SNAKE VENOM,
AND SOME STUDIES OF ANTIVENINE.

JOSEPH McFARLAND, Philadelphia, Pa.

In order to determine whether the experimental immunity to serpents' venom, upon which Calmette has done such interesting work, applied equally well to venoms of the cobra and rattle-snake, I began, about two years ago, to endeavor to immunize several horses to the venoms of American rattle-snakes.

The problems encountered were more difficult than those with which Calmette had to contend, because of the intense local irritative action of the venom. Cobra venom possesses this local irritative property in very slight degree, and Calmette found that when the cobra venom was heated to 70° C. for an hour, it was completely set aside. I found, however, that when rattle-snake venom was heated sufficiently to annul its irritative qualities its toxic properties were almost destroyed. My horses at first received heated venom, but later were injected with solutions of the dried venom in its normally active state. The injections were given subcutaneously and were followed by enormous edemata, necroses, and sloughs, so that after determining that no immunity to the local action developed, this method was abandoned and the intravenous method used. The interior of the vessels showed no sign of injury, probably because the well diluted venom at once met with greater dilution in the circulating blood. No local or other irritative disturbance followed the intravenous injection, but the nervous impression was profound, and the horses often fell, and remained unconscious for some minutes after injection, and, to prevent injury to themselves, required to be suspended.

Two of three horses died before antivenine developed, from the damage to their tissues caused by the irritation of subcutaneous injections. The third horse lived for a long time, and developed a very marked immunity associated with the appearance of antivenine in the blood. The death of the horse finally resulted from the unfortunate accidental en-

trance of some venom into the sheath of the jugular vein during one of the injections. Not being immune to its irritant effects, the venom produced a local edema which killed the animal by suffocation.

The antivenine produced by this horse was of such strength that two cubic centimetres of the serum protected a rabbit—an adult rabbit—against a fatal dose of either rattle-snake (0.002 gramme) or cobra (0.001 gramme) venom.

HOW CAN BACTERIA BE SATISFACTORILY PRESERVED FOR MUSEUM SPECIMENS?

H. W. CONN, Middletown, Conn.

A method of preparing museum specimens was described. A two per cent. agar culture medium is placed in large test tubes and tilted so as to make agar slants. The tubes are left undisturbed for from six to eight weeks, in order to allow the surplus moisture to evaporate. They are then inoculated in long streaks and immediately sealed with plaster of Paris and paraffin: the cultures grow for a few days, then cease growing and remain unaltered indefinitely. No disinfectant is needed. The cultures remain alive for many months, and possibly for years. The method is satisfactory except for one fact: the atmosphere in the tube becomes filled with moisture and this condenses on the inside of the tube with changes of temperature. No method has yet succeeded in avoiding this condensation of water, which in most cases renders the tube cloudy, and injures its value as a display specimen.

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AN APPARATUS AND METHOD FOR RAPIDLY STAINING LARGE
NUMBERS OF SPUTUM SPECIMENS.

BURT RANSOM RICKARDS, S.B.

(Assistant Bacteriologist, Boston Board of Health Laboratory.)

In May, 1900, the Boston Board of Health instituted the compulsory notification of pulmonary and laryngeal tuberculosis. In order to facilitate the diagnosis of this disease, the bacteriological laboratory undertook free sputum examinations for physicians. During the nine months commencing May 1, 1900, over one thousand specimens were examined.

At first, the ordinary slide-and-cover-slip preparation answered all purposes. As the number of specimens increased, however, it became apparent that a shortening of the time required in making a preparation was not only desirable, but would sooner or later become a necessity in order that the laboratory might successfully cope with all demands made upon it.

With this end in view, I designed the apparatus shown in the drawing. (Fig. 1.)

The apparatus consists of a long narrow copper bath mounted on legs which are inclined and terminate at a broad

base weighted with lead to ensure sufficient stability. At one end near the top are two inlets; the upper one (A) for the admission of the stain, the lower (B) for water. In the bottom of the bath (at the same end) is a small outlet (C) for the stain, closed by means of a rubber tube and pinch-cock. At the other end of the bath, partitioned off by a false wall, is a one-half-inch siphon, the inner end of which is left at least three-eighths of an inch from the bottom to prevent the effect of capillarity. The top of the siphon is about on a level with the upper inlet. Guides are placed at each end of the bath proper. The bottom of the bath is eight inches above the base, allowing room for a Bunsen burner. The entire apparatus is nickel plated.

Instead of the ordinary small microscopic slide, a piece of thin plate glass (nine inches long by three wide) is used. It is etched with hydrofluoric acid as shown in the diagram. (Fig. 2.)

The etched area above the spacings furnishes a roughened surface on which the names of the patients can be written with lead pencil, or, better still, with a Faber blue pencil, made especially for writing on glass. This serves to identify the specimens. The slide slips easily into the bath and is held upright by the guides at the ends. Since the slide is three inches wide and the bath but two and one-half deep, one-half inch of the slide projects above the top of the bath, furnishing a convenient means of handling it. Each slide has space for ten or twelve specimens. Thus thirty specimens or more can be stained at one time.

Carbol fuchsin and Loeffler's methylene blue are used as the stain and counterstain, with 3 per cent. hydrochloric acid in 95 per cent. alcohol as the decolorizer.

The technique employed is as follows:

By means of a rubber tube and siphon attachment carbol fuchsin is admitted from the stain bottle through the inlet (A) into the bath until it is about two-thirds full, or until the stain has reached the lower edge of inlet (B). This depth is sufficient to cover the preparations without starting the siphon.

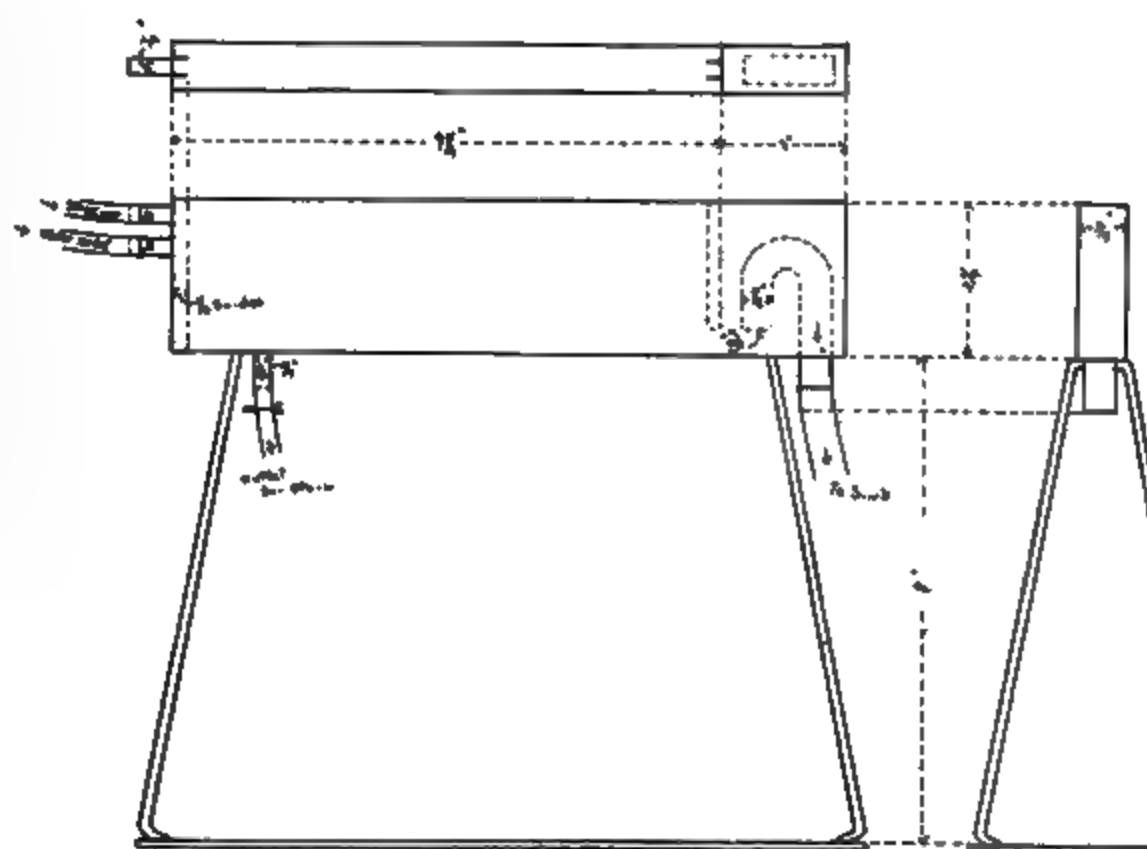


FIG. 1.

Staining Bath for Sputum Specimens.

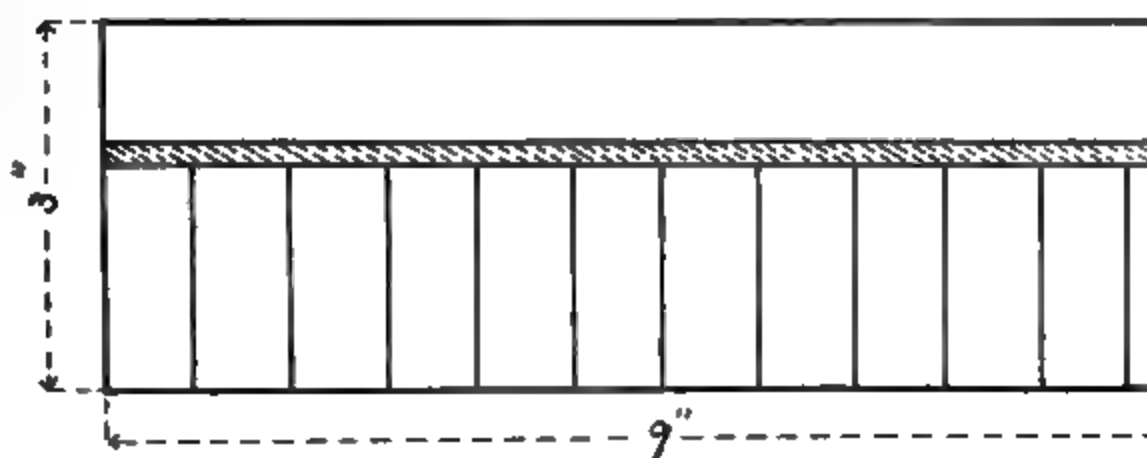


FIG. II.

Slide for Sputum Specimens.

An ordinary Bunsen burner with a wing tip may be used to heat the stain to the requisite temperature.

While the stain is heating, the specimens for examination are smeared and dried. The slide is then placed in the bath.

As soon as the specimens are stained sufficiently (about four minutes at 50° C. being used in this laboratory), the carbol fuchsin is drawn off through outlet (C) into a bottle kept for this purpose. It is well to have the two stain bottles of the same size, so that when the one used for receiving the stain becomes full, it can be exchanged for the one connecting with inlet (A).

Water is then turned into the bath through the lower inlet (B). The bath fills until the top of the siphon is reached, then drains rapidly and almost completely, leaving but three-eighths of an inch of water in the bottom. The siphon breaks and the bath again fills and empties, and so on. By means of this intermittent filling and flowing the slide is washed quickly and completely, without requiring any further attention.

When the washing is complete the slide is taken from the bath, and the preparations decolorized. For this purpose is used a glass candy tray, which is a trifle over nine inches in length, and wide enough to contain two slides side by side. At the ends of this tray small strips of glass are cemented to the bottom. The slides are placed in the tray, specimen side down, the ends resting on the glass ledges. These ledges serve two purposes,—they prevent any scraping of the preparation by contact with the bottom of the tray, and they economize the decolorizer. The solution is drawn beneath the slide by capillarity, and can be made to flow back and forth by tilting the tray. Thus it is necessary to use but a very small quantity.

After decolorizing, the slide is again placed in the bath and washed. It is then withdrawn, dried, stained with methylene blue, and examined.

The advantages of this apparatus may be summarized as follows:

(1.) Economy of time; thirty specimens can be stained as quickly as one specimen. During staining and washing, the operator's attention can be devoted to other things.

(2.) Cleanliness; doing away with spattering of staining solutions.

(3.) Adaptability; obviously a bath of this kind can be used for many different laboratory purposes.

THE INOMOTOR.

A Fundamental Mechanism for a New System of Motor Vehicles, Testing Apparatus, and Developing Appliances.¹

D. A. SARGENT,
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Some twenty years ago I came to the conclusion that certain radical changes were necessary in the aims, methods, and equipment of the gymnasium in order to make it serviceable for all classes in the community. At that time I had had several years' experience in teaching gymnastics and in observing the results of their practice in two college and two large city gymnasiums. I had seen men turned away from these institutions by the score because there was nothing pleasurable or profitable that they could do. The heavy work was too heavy and exhausting; the light work was too light and spiritless, and the acrobatic work was either beyond the ability of most persons or very distasteful to them. In order to meet what seemed to me the urgent need of the times I had a great deal of the old-fashioned apparatus remodelled, and introduced the modern system of pulley weights and developing appliances. This new apparatus immediately opened up the possibilities of the gymnasium to those to whom it had hitherto been a closed institution. It sprang into popular favor at once, and every well-equipped gymnasium in the country is now supplied with this kind of apparatus. As a means for strengthening weak parts, correcting physical defects, and giving one an all-round development of the whole muscular system, no class of apparatus can compare with the chest weights and the numerous pulley weight appliances. The principal reason why this class of apparatus is superior to all others as a means of muscular development

¹ This paper was also read at a meeting of the Boston Physical Education Society at the Hemenway Gymnasium, Harvard University, Monday, Dec. 3, 1900, and published in the "American Physical Education Review."

is because by the use of the pulley, the weight or resistance to be overcome can be met or applied in all directions, and can be readily adjusted to the weakness of the weak as well as to the strength of the strong.

But no single class of exercises is perfect in itself, and there are some objections to the pulley weight appliances if depended upon solely. The exercises are apt to become a little monotonous to persons who feel that they must have some immediate object in view, like a real or imaginary opponent, in order to induce them to make any earnest physical effort. To those who have sufficient morale, and they are many, to hold themselves down to a particular line of work in order to insure their physical improvement, and prepare themselves for the anticipated joys and pleasures of a useful life, this objection of course does not count. Two better founded objections may be brought against the pulley weights as perfect forms of exercise, and it is a little strange that the opponents of the system have never discovered them, though pulley weights for exercising purposes have been in use in this country in one form or another for over thirty years. If one wishes to attain a high degree of speed and great rapidity of movement this power cannot be gained as effectively through the pulley weights as by the use of some other kind of apparatus, as the punching bag and light dumb-bells. A weight attached to a cord is always limited to the velocity of a falling body through the distance which it is raised so long as the cord is kept straight. As the cord must be kept straight in order to keep the weight from jerking it in a disagreeable manner, and as the range of the movement which the body is capable of making limits the height which the weight can rise and fall, the speed with which it can be made to rise and fall is not great enough to call forth a very rapid contraction of the muscles. The practical limit is about one stroke a second for each arm. Of course this failure of the weight to rise and fall fast enough to afford a speedy contraction of the muscles may be overcome somewhat by the use of springs or rubber cords, but this introduces another factor which is more objectionable than the

first, and calls for a more extended explanation which it is not necessary to make at this time. The principal objection that may be brought against the pulley weights is one that is common to dumb-bells, Indian clubs, and many other kinds of portable apparatus; that is, these forms of exercise are essentially local in their effects rather than general. It is this very fact, however, that makes the pulley weights so valuable in correcting physical defects and developing weak parts of the body. But it is possible to develop one part after another until a man becomes very strong all over, and yet be decidedly lacking in ability to make continued application of his power for any length of time. Perhaps this is the most frequent as well as the most serious defect of well-developed men. They often acquire their general muscularity by local instalment, as it were. If called upon to bring a great many muscles into action at one time they are very much distressed for breath, and show an unwonted amount of cardiac excitement. This condition of affairs may be due to interference with respiration through excessive chest and shoulder development, or to the fact that development of the heart and lungs has not kept pace with the development of the general muscular system. A man in this condition is like a factory that has been accustomed to work but a few of its machines at one time, and has an engine adapted to that purpose. In case all the machinery is started up at once, the boiler cannot generate steam enough to supply each machine with its requisite amount of power, and consequently permits of little effective work being done by any one of them. The remedy for the factory is to build a larger engine, or generate more steam. In the case of an individual the remedy is to invigorate the heart and lungs and, if possible, give more nerve power. The best kinds of exercise to produce these results are rowing, running, and swimming, because they bring so many muscles into action at the same time. For this reason the pulley weight appliances, with their strength-giving qualities, should always be supplemented by the practice of some good constitutional exercises, like rowing, swimming, etc.

But unfortunately our climate does not permit of these exercises all the year round, and we are driven by necessity to resort to other methods for attaining this increase of heart, lung, and nerve power. After several years of experimenting I have settled upon a system of mechanical devices, which are designed to meet this long-felt want.

As I have said before, one of the criticisms that is frequently made against the developing apparatus of the gymnasium is that the exercises are monotonous, and have no element of pleasure or excitement about them, such as is afforded by races and competitive sports and games. Realizing that this criticism is to a certain extent just, an attempt has been made to supply the element of pleasure and excitement by having some apparatus so constructed that the exercise taken with it sets it in motion, thus affording an opportunity for competition in different kinds of races on the floor of the gymnasium, as rowing, paddling, sculling, etc. By reducing the gear for indoor uses and competitive purposes, the apparatus may be made to record so many feet to the mile, while the same kind of apparatus may be geared up to allow of considerable speed where there is plenty of room on roads and tracks out-of-doors. Up to the present time the bicycle seems to be the only mechanical contrivance that has been used successfully for locomotive exercise. Various attempts have been made to propel vehicles of one kind or another by hand or foot power, either singly or combined, but for one reason or another all of these attempts have been abandoned, and to-day, in spite of the demand for some such mechanism, there are but very few in existence. The bicycle is about the only one that is much used. Does this meet the demands of the body for exercise and development?

Several years ago in the course of my professional experience, I made a physical examination of a young and promising student. He had dark eyes, an unblemished pink and white skin, and a pair of legs that would have gladdened the heart of a sculptor. His chest and arms, however, were poorly developed and presented a pitiable contrast to his

finely-lined and well-formed lower extremities. Upon my inquiring of him why he did not pay more attention to the development of his arms and chest, he calmly replied, "Arms and chests do not win bicycle races." Suffice it to say that his ambition was to win distinction as a bicycle rider, and with this end in view he made bicycling his only form of exercise. He won one or two records at that time and one year the college championship, but he died of consumption a year or two after graduating. In my opinion, the young man could have been saved from an early grave if he had devoted more attention in his college days to the development of his lungs and chest. Bicycling has undoubtedly done much to improve the health of our civilized communities, mainly by inducing many persons to take exercise who never took any before, by carrying them out into the country where they get the benefit of fresh air and sunshine, and a change of life and scene. The bicycle also teaches self-control, which is one of the first requisites of good physical training.

In order to make bicycling attractive as an exercise it has been found necessary to make it so easy that the wheels almost go by themselves. The artisan has so improved the mechanism of the machine that friction has been reduced to a minimum, and only the smallest amount of power, a draw bar pull of about four pounds for the average man, is necessary to propel a bicycle on a good, level road. Century runs are so common that they are not only made frequently by ordinary men and women, but even by children of nine and ten years of age. The ability to cover such distances in a short space of time is not due to any sudden increase in the strength and endurance of the race, as one might infer, but is simply another tribute to the skill of the man who has modelled such a machine. It is just this factor that has made the modern bicycle an indispensable adjunct to every household as a time-saving, strength-conserving, useful agent. But the ease with which the bicycle can be propelled and the very few muscles which are engaged in the operation lessens its value as a means of physical exercise and development. In

ordinary riding the muscles of the arms, chest, shoulders, back, and abdomen have little or nothing to do, all of the work of propelling the machine after the art is acquired coming upon the extensors and flexors of the feet and legs. With most persons the arms are used simply as guides to steer with, or as props to hold the body erect. The chest muscles remain comparatively inactive, and the muscles of the back and abdomen being relieved by the arms of their function of balancing the body, may actually pine for the want of more work to do. A faulty position long maintained soon results in a permanent drooping of the head, elongation of the neck, rounding of the back and flattening of the chest, all physical defects which are now far too common. Where children begin to ride at an early age and depend upon bicycling only for their exercise, malformations are acquired, and deficiencies in growth become established which are very difficult to eradicate. My attention has been frequently called to these cases, and I have long felt the want of something outside of the gymnasium that would supplement the bicycle in affording a more perfect means of all-round physical exercise.

I had long since observed in making physical examinations that the best specimens of all-round physical development were, as a class, among the rowing men. Since the introduction of the sliding seat, rowing, of any single sport, undoubtedly furnishes the best exercise for the whole body. A brief analysis of the act of rowing makes this fact perfectly apparent. Let us start with the beginning of the stroke. The oar is grasped by the hands and held in place by the flexors of the fingers and wrists, which are on the forearm. In bringing the body into an erect position the muscles of the back, buttocks, and hips, and hamstring muscles of the legs are brought into powerful action; then as the feet are pressed against the stretcher and the seat is started backward on its slide the muscles of the calf and the extensors of the legs are brought into play. In the meantime the arms which are pulling at the oar are being brought backward by the contraction of the trapezius, the muscles between

the shoulder blades and the latissimus dorsi, the broadest and strongest muscles of the back, which are attached to the bones of the upper arms. Then just as the stroke is finished the biceps or flexors of the arms, and extensors of the wrists, are used to pull the oar through and feather it preparatory to the next stroke. At this juncture the oar is pushed forward by means of the triceps, anterior deltoid at the shoulder, and pectoralis major on the chest; then the flexor muscles of the feet and the flexors of the legs and thighs contract to draw the pelvis forward with the sliding seat, while the abdominal muscles are working hard to bring the body from the leaning-back posture, assumed at the finish of the stroke, into the upright position, and carry it forward ready for the next stroke. In bringing the body to an upright position the abdominal muscles are aided by the contractions of the psoas magnus and iliacus, two muscles that come down from the inner side of the lower spine and pelvis, and are attached to the thigh bones. As the body swings forward the shoulder blades are moved apart by the serratus magnus and the arms are extended to a position of full reach, so that the hands are beyond the toes, where they are ready to dip in the oar for the commencement of another stroke. Thus it will be seen that in the act of rowing most all of the important muscles on the front and back of the body and limbs are brought into action. It is for this reason that rowing is such an admirable exercise for developing the heart and lungs. So many muscles are used that the heart and lungs are forced to work harder in order to get rid of the increased amount of waste product and to supply the muscles with their necessary nutriment, so that the respiration, circulation, and assimilation of the whole body are greatly improved.

In attempting, therefore, to devise an exercising machine that would give employment to all of the important muscles, something which would permit of a resemblance to the rowing movement seemed almost necessary. But rowing, critically examined, has some serious defects both from a physiological and from a mechanical point of view. While it

brings many muscles into action, it requires a person to use many of them in a cramped position, and to a great disadvantage, as in case of extreme reach of the arms forward. The whole work must eventually be done through the arms and hands, just as the work in bicycling finally comes upon the feet and legs, whatever assistance may be rendered by the rest of the body. The sliding seat enables the person to get a great reach forward at the beginning of the stroke without cramping the body quite so much, but the power communicated to the oar must be given to it through the arms, which then transmit it to the shoulders and down the back to the pelvis, from which it is transmitted through the legs to the stretcher, where the final effort, but for the oar in the water, would be to drive the boat astern. On the other hand, the effort of the feet in the toe-straps to pull the seat back really tends to pull the boat forward, but the principal effort of the recovery is an effort to get the body forward so as to begin the work of the stroke. As a matter of fact, two-thirds of all the muscular power used in rowing is lost because it cannot be directly applied. This effort undoubtedly gives exercise to the muscles, but so much of the energy put forth is lost in friction and in heat that the effort, if long continued, becomes wearisome and exhausting.

In this new mechanical device or invention, to which the attention of the public is invited, I have endeavored to introduce a new principle into the art of propelling land or water vehicles, of using gymnasium machines for developing purposes, and of applying human power so as to realize the greatest amount of work. In devising this mechanical arrangement I have had several correlated objects in view.

1. The invention of a machine that will afford the best means of strengthening and developing the principal muscles of the body.

2. A machine that will permit of the use of the muscles in a perfectly natural way, each group according to its strength.

3. A machine that will bring so many muscles into action at one time as to develop the heart and lungs, without

causing distress through vigorous efforts made in faulty positions.

4. A machine that will make exercise pleasurable and enjoyable through its beneficial influence on the entire system.

5. A machine so constructed that every movement of flexion and extension in trunk, legs, feet, and arms adds to the propelling power.

6. A machine that will admit of one group of muscles being used while others are relaxed, or of one part of the body to rest while another part is being brought into action, or of legs, trunk, and arms being used simultaneously, or of all the important muscles being used in succession.

7. A machine that could be used for the reduction of fat or obesity through general muscular activity without obliging the individual to support his own weight and thereby strain the muscles and tendons of the feet and legs before the rest of the body has had exercise enough to bring about a vigorous circulation and respiration.

8. A machine that would act especially upon the back, waist, and abdominal region, which I have come to consider the weak points of many of the American people of both sexes.

9. A machine that would tend to correct the drooping head, rounded shoulders, and flat chests, which characterize so many of our school children, students, literary men, and those who pursue a sedentary occupation.

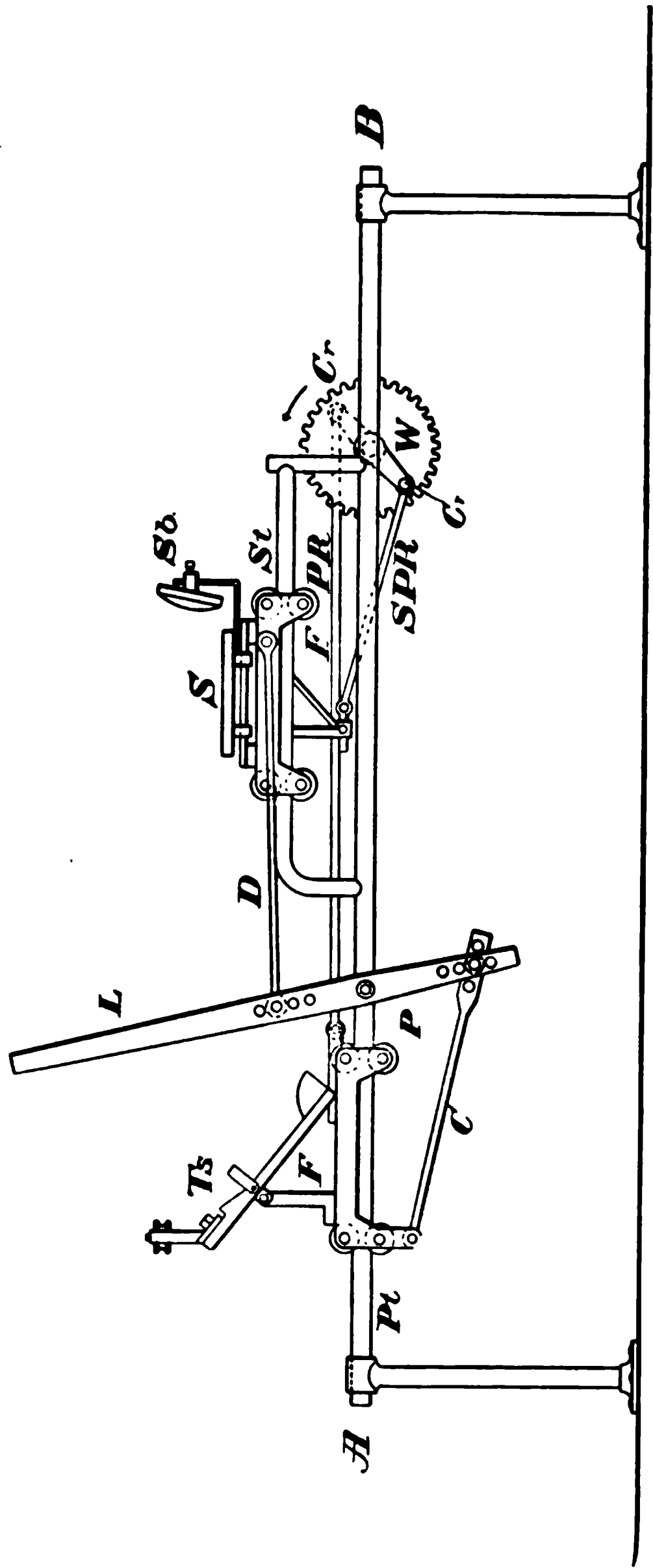
10. Finally, a machine so constructed that it is almost a gymnasium in itself that can be used indoors or out-of-doors, and that can be applied to the propulsion of vehicles on the land, ice, or snow; or to the propulsion of boats, by means of oars, paddle-wheels, or propellers.

The mechanism which I have contrived for the accomplishment of these several objects, and which I have termed an inomotor, may be described in its simplest aspect as a pair of levers connected by four adjustable rods with a sliding seat, and a sliding foot rest, which are each in turn connected by a power-applying rod or cord to a crank clutch gear or sprocket wheel.

A more careful consideration of this mechanism will show the details upon which its efficiency as a power-applying machine depends. (See Plate XXXV.)

A B is a frame work composed of steel tubing. L represents a hand lever pivoted at the point P. F is the travelling foot rest which moves upon the track Pt, and S the travelling seat which moves upon the track St. W is the gear or sprocket wheel, one crank of which is connected with the foot rest by the rod FPR, and the other crank is connected with the seat frame by the rod SPR. The hand lever is connected with the foot rest by the rod C and with the seat frame by the rod D. The other important parts of the machine are the toe straps, and supports Ts, the seat back Sb, and the double rollers on the foot rest and seat frame.

The action is as follows: The person sits upon the seat S, which is slightly hollowed like a rowing seat to fit the form, and places his feet on the foot rest, sliding the toes of his boots well up under the toe straps Ts. He then leans forward and grasps the hand levers L with his hands while the arms are extended. He is now in position to begin the stroke. As he pulls backward on the lever L he instinctively braces his feet against the foot rest for support as in rowing, but the moment the foot rest begins to feel the power exerted on the levers by the hands, it moves forward as it is connected with the levers by the rods C; the pressure of the feet therefore upon the foot rest only tends to hasten and intensify its movement forward. But as it goes forward it turns the wheel W half round through its connection with one of the cranks by the rod FPR. Simultaneously with the effort to pull the hand levers backward and brace the feet against the foot rest, the seat is carried backward by the rods D, which are connected with the hand levers, and the pressure of the pelvis against the seat back Sb, which results from the pressure of the feet against the foot rest and the extension of the legs. But when the seat S goes backward the wheel W is assisted in making a half revolution through its connection with the seat frame by the rod SPR. By this time the hand levers have been brought well back toward the



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seat, the legs have been fully extended, and the seat and foot rest are as far apart as possible. As the body inclines back of the perpendicular the toes bend up under the toe straps, and as the foot rest feels the pull of the feet and legs it begins to return to its starting position. In so doing it is greatly assisted by the powerful impetus that may be given to it by a forward push of the handle bars. When this takes place the seat is pulled forward and the foot rest is pulled backward by the rods D and C, connecting them with the handle bars, and thus the wheel W is made to complete its revolution by the action of the rods SPR and FPR. The wheel W may be connected with other gear wheels and thus movement may be given to friction wheels, or fly wheels on stationary machines, or to paddle wheels, propellers, or driving wheels for general locomotion. Applying the power by a pair of levers placed in a vertical position about the width of the shoulders, or 18 inches apart, enables the person to support his body in an upright position without the constant tendency to slump or bend forward at the waist, which is so frequently experienced in rowing and bicycling.

The handle bars have a leverage of about five to one, and the power that can be exerted by a direct drive from the legs by aid of the seat back is more than three times as much as the legs can exert when the strain is transmitted through the back and arms, as in ordinary rowing. Moreover, more power can be applied to the vertical levers with the arms parallel and the chest free than with a horizontal lever, with the hands close together and the chest walls more or less cramped or restricted in their movements.

It will be observed in working the apparatus that the greater the strain put upon the handle bars by the hands, the greater will be the force exerted upon the foot rest and seat frame by the feet and legs, and consequently the greater will be the power communicated to the gear wheels. This is equally true of the backward or forward movement, and when both hands and feet are working it involves the flexion and extension of the forearms, upper arms, legs, thighs, and trunk, which brings into action all of

the important muscles of the body. It will also be observed that on account of the union of the foot rest and seat frame with the handle bars and gear wheel, through the agency of the connecting rods, any movement communicated to one part is communicated to all parts. Thus the levers may be worked by the feet and legs, while the arms and trunk are at rest, or the arms and trunk may keep up the work while the feet and legs are passively flexed and extended by the movement of the foot rest and seat frame. Moreover, if it is desired to use any one part of the body more than any other as a means of strengthening and developing it, this may be done by making this part do more than its usual share of work. Considering the nature and number of parts used, it will be seen that the apparatus can easily be employed as a means of special development for the biceps, triceps, shoulders, upper back, lower back, chest, abdomen and waist, gluteal muscles, front thigh, back thigh, calf and front leg, as well as a means of general development for all these muscles combined. The value of the machine as a corrective agent for physical defects and weaknesses is thus made apparent.

The machine is so constructed to admit of as little lost motion as possible. In whatever direction arms, feet, legs, or trunk may be moved, the effort is converted into a mechanical advantage which is always contributing to the revolution of the gear wheels. Where it is desirable to have the active efforts followed by a certain amount of passive exercise, larger fly wheels may be used on the gymnasium machine. The momentum acquired by the rapid revolution of these wheels will flex and extend the arms, trunk, and legs for a considerable time without any active efforts, thus favoring the returning circulation of the blood and removing the cause of fatigue when it has been produced.

The gymnasium machine also may be so used as to allow the operator to oppose one set of muscles to another, and thus add to the resistance to be overcome at any part of the exercise. Thus the action of the chest muscles, abdominals, and the extensors of the forearms may be intensified by

resisting the tendency of the handles to come backward, when they are impelled through their connection with the seat by the powerful extensors of the legs. So the flexors of the arms and extensors of the back may be opposed to the flexors of the feet and thighs, etc., etc. This use of the machine is of course greatly favored by the action of the heavy fly wheels or the momentum acquired by the motor vehicle.

Where great rapidity of movement is desired, followed by absolute rest, a clutch wheel is used in place of the cranks and spur wheels. If it is desirable this allows the extensors of the back and legs to work with great speed and intensity, while the flexors of the thighs, legs, and abdominals and the extensors of the arms and the chest are only engaged in drawing the body forward and shooting the arms out preparatory to another stroke, as is the case in rowing. The machine may also be so used as to just reverse this process. When it is desirable to attain more resistance for the powerful extensors of the legs and back an elongated spiral spring may be used to supplement the resistance furnished by the machine. The use of the spring will greatly aid the return of the handles to the starting position, thus relieving the chest and abdominal muscles of any undue strain.

Some of the special applications of this device, with illustrations of other forms of apparatus evolved from it, will be considered later.

ON THE SUPPOSED ACTIVITY OF CORN SMUT. ¹

A. W. BALCH.

(Assistant in Pharmacology, Harvard Medical School.)

Corn Smut was described in the United States Pharmacopœia of 1880 as being the spores of *Ustilago Maydis*, parasitic on various parts of Indian corn.

It has been believed, not only by the laity, but also by the medical profession, to be similar in action to Ergot of Rye, and for this reason has been called Corn Ergot.

That the supposed value of the substance had many adherents is shown by the fact that the smut was official in the Pharmacopœia of 1880.

It has been claimed by farmers that cattle fed upon corn and corn stalks which contain the smut have died as a result of its toxic action.

Several attempts have been made at isolation of an active principle from corn smut, but the results obtained are very unsatisfactory.

C. H. Cressler ("American Journal Pharmacy," 1861, p. 306) found, in smut, a crystalline substance which was precipitated by lead acetate, a volatile alkaline substance which he claims to be propylamine on account of the odor, and a substance which he called "secalin," of which no properties are given.

H. B. Parsons (Report of the United States Commissioner of Agriculture, 1880, p. 136) found a substance which he called sclerotic acid, but no analysis was made. Sclerotic acid was prepared by exhausting smut with water after extraction with alcohol and ether. The aqueous solution was concentrated, treated with an equal volume of alcohol, and the mixture filtered. To the filtrate a large amount of alcohol was added, when the sclerotic acid was precipitated in considerable quantity.

The research was carried out with the aid of The Elizabeth Thompson Science Fund.

Rademaker and Fischer ("National Druggist," 1887, p. 296) found two per cent. of sclerotic acid in smut, and state that it is soluble in alcohol, ether, and water. No method of preparation is given. The sclerotic acid of Parsons was insoluble in alcohol and ether. Rademaker and Fischer also obtained by dialysis of an alcoholic extract from which alcohol had been removed and to which sulphuric acid had been added, a crystalline alkaloidal substance, the analysis of which was not made.

We know from the experiments of Recklinghausen and Kobert ("Archiv. f. exp. Pathol. und Pharmacologie," 1884, p. 331) that certain species of animals are susceptible to the toxic effects of Ergot of Rye, while others seem to be immune toward this drug. The animals which according to these authors are especially suitable for the demonstration of ergot poisoning are the barnyard cock and swine. In these animals a hyaline thrombosis is produced, and this is followed by gangrene in certain parts. So far as we know, no experiments have been made with corn smut upon these animals.

It was determined, therefore, to examine the smut chemically to see if the experiments of others could be sustained. These experiments failing, we purposed to experiment upon susceptible animals by giving them large quantities of corn smut for prolonged periods of time to see if the characteristic action of Ergot of Rye could be produced.

For the chemical experiments a large number of different specimens of smut were obtained from different parts of the country. The fresh smut was collected in the country about Boston. Extracts were prepared with naphtha, ether, alcohol, and water, and each extract separated into two parts by precipitation with lead acetate. The lead was removed from each part by hydrogen sulphide, and the products were again extracted with each of the above solvents.

The residues obtained by evaporation of the solvents from the various solutions were tested in frogs by injection of large doses into the abdominal cavity, but in no case was the substance found to be active.

Evaporation of the alcohol from the alcoholic extracts

left an oily residue. From this the oil was removed after addition of water, and it was found that the aqueous fluid contained a considerable amount of insoluble matter in suspension. This suspended substance was soluble in alcohol, and from the alcoholic solution, when diluted largely with water, it was precipitated as white crystalline needles. The substance was obtained pure by repeating the above process of purification. The substance is soluble in alcohol, chloroform, ether, and amyl alcohol, is very slightly soluble in hot water, and is insoluble in cold water and naphtha.

The solution in hot water has an acid reaction, and the lead, silver, magnesium, barium, and mercuric salts are insoluble in alcohol and water. The melting point is 96.5–97.0 C.

0.05 G. of the sodium salt was injected into the abdominal cavity of a frog. Death followed two days later, no symptoms having been noticed before death.

0.100 G. of the sodium salt was injected subcutaneously in a pregnant guinea-pig. No action was obtained.

Attempts at isolation of an active principle having failed, it was determined to administer the crude substance in the endeavor to obtain some action.

The drug was administered to cocks in the form of pills made from the crude substance and from both the aqueous and alcoholic extracts.

The smut was obtained from dealers in different parts of the country.

The fresh fungus was collected and given as such and after being dried in the laboratory.

Both green and mature masses were used.

In a few cases the comb, and more rarely the wattles of the cock showed some degree of darkening, and in exceptional cases the whole comb became quite black.

The color never persisted for more than a few hours and no other effects could be seen.

The feeding experiments are appended in the form of tables.

20 days, each, 1.0 G. Smut.
7 days, each, 1.5 G. Smut.
6 days, each, 2.0 G. Smut.
9 days, each, 2.5 G. Smut.
25 days, each, 3.0 G. Smut.
1 day, each, 3.5 G. Smut.
12 days, each, 6.0 G. Smut.
3 days, each, 6.75 G. Smut.

This period lasted 83 days, and during the time 235.75 G. of smut were fed to the animal. The comb occasionally showed a slight degree of darkening, and this was also seen during the following twenty-one days when no smut was given.

In the next experiment made upon the same animal, the dose was increased.

3 days, each, 6.75 G. Smut.
4 days, each, 9.0 G. Smut.
4 days, each, 20.0 G. Smut.

During this period the comb showed considerable dark color soon after the smut was given, but the color never persisted.

Forty grammes from a new lot of smut were then made into 178 pills, and 150 pills were given in one day. No effect could be seen.

Four hundred and forty pills were then made from 80 G. of still another lot of smut.

The first day 90 pills were given, the second day 120 pills, the third day none, and finally 90 pills on each of the two following days, without effect.

Commercial specimens of smut thus proving to be inert, it was decided to try recently collected smut, dried in the laboratory.

Seventy grammes of this were made into 273 pills, which were given as follows:

1 day, 30 pills.
1 day, 90 pills.
1 day, 60 pills.
1 day, 90 pills.

No effect was observed.

Twenty-eight grammes of fresh smut prepared in the same way were made into 113 pills and tried as follows on a new animal:

1 day, 24 pills.

1 day, 8 pills.

3 days, each, 27 pills.

After the administration of the first lot of pills in this experiment the comb became quite dark, and some darkening was observed after dosage on the two following days, but in no case was the color persistent.

Thinking that the activity of the drug in these last experiments might have been impaired through the process of drying, it was decided to administer fresh smut.

This was done as follows:

Twelve grammes of fresh smut were made into 27 pills.

1 day, 6 pills.

4 days, each, 9 pills.

1 day, 10 pills.

Forty grammes of fresh smut were made into 75 pills.

1 day, 24 pills.

1 day, 36 pills.

1 day, 15 pills.

No effect followed these experiments, showing that the lack of action in the previous experiments was not due to the drying.

We now decided to experiment with unripe masses of smut dried in the laboratory.

Forty grammes of this were made into 168 pills, which were fed as follows:

3 days, each, 9 pills.

1 day, 20 pills.

2 days, each, 60 pills.

This was also without effect.

Wishing to increase the dose, we now prepared an alcoholic extract from 500 G. of smut, and this was given at a single dose.

A similar dose was given on each of the five following days.

A slight darkening of the comb followed one of these doses, but no other effect was seen, in spite of the fact that the extract of 3,000 G. had been given.

From an aqueous extract of smut an alcoholic extract was prepared, and from this pills were made of such size that each represented 5 G. of smut, and given

6 days, each, 12 pills.

3 days, each, 18 pills.

No effect was seen.

An alcoholic extract was then prepared by exhausting the smut with alcohol and evaporating the solvent at a low temperature. The oily extract was given in emulsion through a stomach tube, no effect resulting.

6 days, each, 9 cc.

1 day, 12 cc.

1 day, 20 cc.

One cubic centimeter of a commercial fluid extract of smut, from which alcohol had been removed by evaporation, was injected in the abdominal cavity of a frog. Two days later the animal appeared to be somewhat abnormal. On the third day 1 cc. of the fluid extract free from alcohol was given, and death followed twenty-four hours later.

The same fluid extract, free from alcohol, was used in another experiment as follows:

First day, 2.0 cc.; 2d day, 1.5 cc.; 3d day, 1.0 cc.; 4th day, 1.0 cc.

The animal remained normal eight days and was found dead on the ninth. Death in this case must, however, be attributed to other causes, as with the larger dose death occurred much later than in the previous experiment, and

frogs rarely survived longer in the laboratory, even when no injection had been made.

That different specimens of corn smut vary considerably in composition is shown by the fact that their extracts contain in some cases a large amount of resinous material, while in others the amount is very small.

The acid substance obtained from alcoholic extracts of smut is not present in three specimens recently examined.

From one of the specimens a crystalline substance, apparently a sugar, was obtained, but it was present in none of the others.

The United States Department of Agriculture published in 1898 (Farmers' Bull., No. 69) the results of experiments in which corn smut was fed to cattle. No variations from the normal condition appeared and abortion was not produced in pregnant cows.

It is stated in the Annual Report of the Bureau of Animal Industry for 1898 that the spores probably act by expanding and thus obstructing the stomach.

Kobert (quoted in Cushny, "Pharmacology and Therapeutics," 1900) found corn smut to be inert.

As the results of this investigation agree with others made thus far, we are warranted in claiming that corn smut is inert, and cannot be used to replace Ergot of Rye in medicine.

SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society.

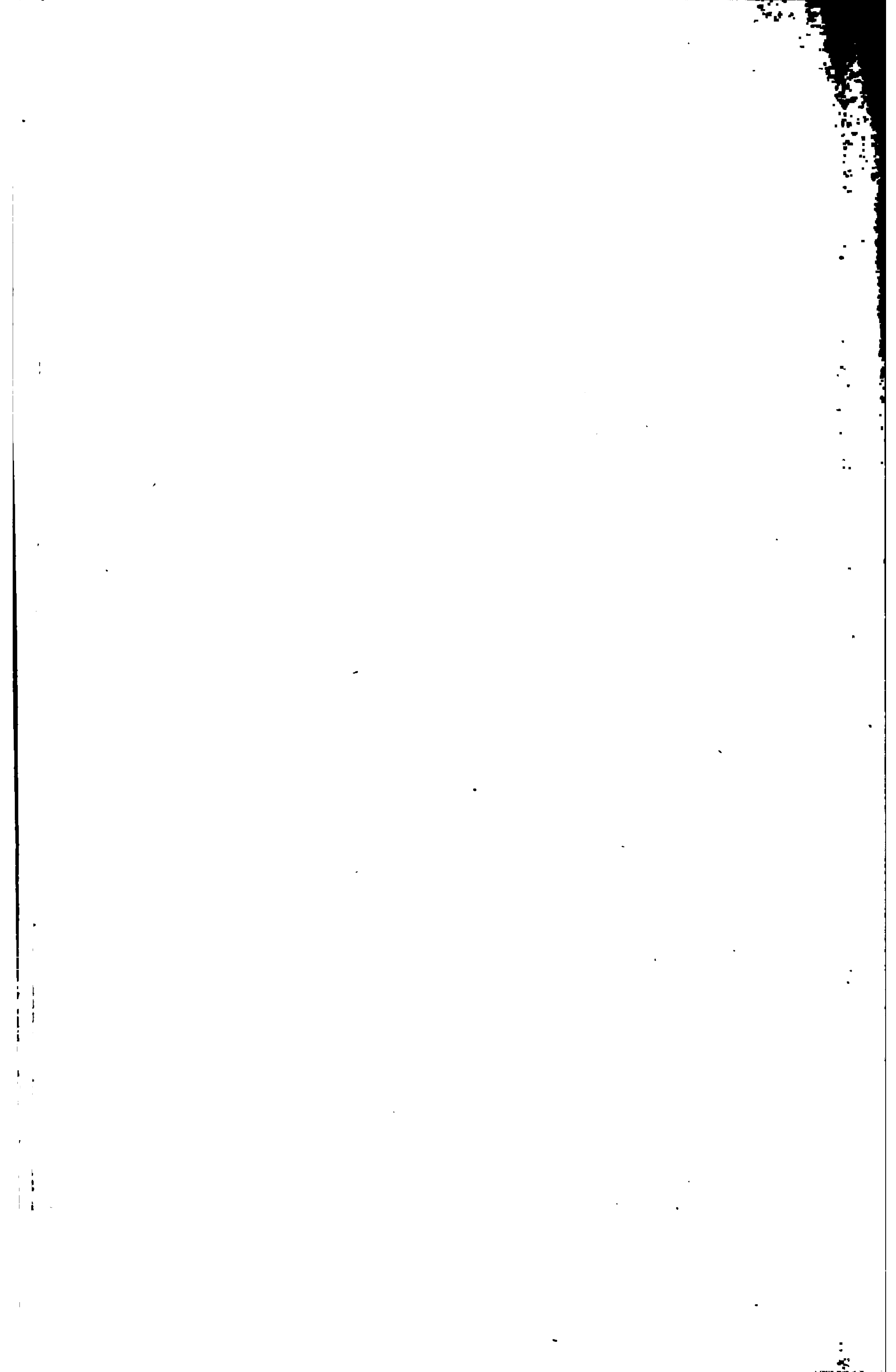
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VOLUME V. No. 9.

APRIL 23, 1901.

A CONTRIBUTION TO THE NORMAL HISTOLOGY AND
PATHOLOGY OF THE HEMOLYMPH GLANDS.¹

Preliminary Report.

ALDRED SCOTT WARTHIN, M.D., PH.D.

(*Assistant Professor in Pathology, University of Michigan.*)

About four years ago my attention was caught by the fact that in certain diseases the prevertebral retroperitoneal lymph glands appeared to play a part entirely independent of that of the other lymph glands of the body. Enlarged glands presenting various striking appearances were found, especially in the neighborhood of the semilunar ganglia, in cases where the other lymph glands showed no change, and where there were no local conditions to account for such findings. Further, the microscopical examination showed that these glands presented a very different histological structure from that of ordinary lymphatic glands, the chief point of difference being that they possessed sinuses containing blood in place of lymph sinuses, as in the case of the latter. From this peculiarity of structure, it was evident that these glands were independent organs belonging to the class already discovered, and somewhat meagrely described as hemolymph glands.

¹From the Pathological Laboratory of the University of Michigan, Ann Arbor.

Since the observations concerning the occurrence and structure of these glands in man were very few and imperfect, and as practically nothing at all concerning their pathology had been noted, the following research along both of these lines was begun, based upon my first observations. The material for this investigation was obtained from my autopsy work of the last four years, 80 cases in all, with but a few exceptions derived from the clinics of the University Hospital. The results of this study have been of very great importance, and touch upon some of the most vital problems in histology and pathology. In this article I shall attempt to give only a preliminary report of these results in the anticipation of a later more complete paper.

Though the hemolymph glands were discovered in 1884, very little work has been done towards fixing their anatomical and physiological position in the human being, in spite of the fact that the possibility of their possessing important blood functions was early pointed out. In the "Microscopical Journal," Vol. XXIV., 1884, H. Gibbes first noticed the existence of these glands in a short paper, "On some structures found in the connective tissue between the renal artery and vein in the human subject." In three cadavers (male, under the age of 30, accidental death; male, aged 58, and another, aged 19, both dying of phthisis) he found glands between the renal artery and vein resembling lymph glands, but differing from them in that they contained blood-sinuses instead of lymph spaces. To these he gave no name, but thought that they were permanent structures. He advanced no theory as to their nature or function, and did not follow up his discovery by any investigations along these lines.

No further mention is made of these organs until six years later, when W. F. Robertson, a student of medicine, working under Dr. Russell in the pathological laboratory of the Royal Infirmary in Edinburgh, made the first detailed description of these glands ("Lancet," Nov. 29, 1890) and gave them the name of hemolymph glands. For the suggestion of this name he acknowledges his indebtedness to Dr. Russell. Of Gibbes' discovery he does not seem to have been aware.

His observations were made chiefly of these glands as found in the sheep and bullock, his studies in the human body being unsatisfactory because of the unfavorable conditions under which the autopsies were obtained. He described these organs as possessing a capsule of dense fibrous tissue and unstriped muscle, thick in proportion to the size of the gland. Immediately beneath the capsule there is a large irregular sinus filled with blood which sends processes into the central lymphoid portion of the gland. The peripheral sinus extends almost entirely around the gland, and its lumen is intersected by trabeculae of a structure similar to that of the external capsule. These freely anastomose and form a scanty network extending from capsule to the central lymphoid portion. The meshes of this reticulum are filled with red blood cells. A similar reticulum is found in the sinuses extending into the central portion of the gland. The lymphoid portion consists of a framework of spindle cells and a small amount of unstriped muscle and elastic tissue. The spaces in the frame-work are closely packed with cells of various kinds, of which he gives a detailed description, calling especial attention to two forms which he very cautiously suggests may be the parent cells of the red blood cells. One of these was a multinucleated cell which as its nuclei increased in number lost its affinity for logwood and became tinged with eosin. The other form was a large mononuclear cell having a small amount of protoplasm and a large nucleus which sometimes contained nucleoli staining with eosin. His histological description was based chiefly upon the structure of these glands as seen in the sheep, where they were constantly found in the prevertebral fat in large numbers, three to four hundred. In man he found them in the same location, but they were not so numerous, and were much more difficult to identify because of the fact that the blood-sinuses are almost always empty, and only rarely distended. According to Robertson, it is, therefore, almost impossible to distinguish with the naked eye between hemolymph glands and ordinary lymphatic glands in the human subject. The microscopic structure of the glands in man he

found to be very similar to that in the sheep and bullock, the chief difference being that the peripheral sinus is frequently interrupted by lymphoid masses reaching to the capsule, and by the fact that the sinuses are empty. The cells of the reticulum are similar to those found in the glands of the sheep. Robertson suggests with caution that these glands are concerned in the formation of red blood cells, but of this he could find no positive proof. He thought that these might be formed in two ways: either from the multinucleated cells becoming gradually changed into blood cells, or that the nucleoli of the mononuclear cells might become red blood cells.

In an article entitled "Report on Hemal Glands," "British Medical Journal," July 25, 1891, Clarkson reported observations on "certain hitherto undescribed glands" found accompanying the renal vessels in the horse, sheep, and goat. No observations were made on the human body. He likewise appeared to have no knowledge of Gibbes' discovery, and while suggesting that these glands have the same function as the hemolymph glands described by Robertson, considers them to be a different variety. According to his description the hemal glands resemble ordinary lymphatic glands, but differ from them in possessing blood-sinuses instead of lymph-sinuses, and containing nodules of lymphoid tissue resembling splenic follicles, but having no artery. He assumes from their structure that these glands are blood-forming organs, but adduces no proof, basing his supposition upon the presence of vacuoles or faintly-staining globules in the protoplasm of certain cells which he took to be red cells in the process of formation.

In the "American Journal of Medical Sciences," 1893, Vol. XXIV., p. 316, Gibbes made a second contribution on this subject. Mentioning Robertson's paper, he says that the latter's description of these glands accords in every detail with the glands described by him in 1884. He accepts the name of hemolymph glands as an appropriate designation for these organs. The fact that his own observations had been confirmed both in man and in the lower animals induced

him to make further investigation with especial reference to the possible occurrence of diseased conditions. He removed all the small structures lying in the connective tissue near the renal artery and vein, in cases of kidney disease, chronic cystitis, stone in the bladder, general tuberculosis, and carcinoma. In all cases he found hemolymph glands, generally more than one on each side. They varied greatly in size, but nothing further was found to add to his former description. In some instances acute inflammatory changes were present, and in a case of general tuberculosis the glands were tuberculous.

Clarkson, in his "Text-book of Histology," 1896, devotes several pages to a consideration of these glands under the heading, "Hemal Glands." He states that they have been observed in the pig, horse, ox, and sheep, but have not yet been found in man, though in his article published in the "British Medical Journal," 1891, he refers to Robertson's paper, in which the occurrence of hemolymph glands in the human body had been reported. He further ignores both papers by Gibbes. He describes two varieties of hemal glands: one small in size and very numerous, and a larger form more nearly resembling an ordinary lymphatic gland and less widely distributed than the first. In the first variety the greater part of the gland consists of blood-sinuses, a peripheral one containing an adenoid reticulum, and large central sinuses without reticulum. The lymphoid tissue between the sinuses is variable in amount and arrangement. Regarding the function of this variety, he says that there seems little reason to doubt that they are local centres for the production of blood corpuscles, both white and red, but the stages of formation have not yet been traced out. This supposition must be taken as being purely hypothetical on Clarkson's part, as he made no observations in any way tending to prove it. He describes the second variety as having somewhat the structure of a lymph gland, except that the medulla appears to be represented by a more or less compact mass of lymphoid cords and the peripheral sinus is filled with blood. This form he found to be especially localized in the neigh-

borhood of the kidneys. Cover-glass preparations from both kinds of glands gave identical results, viz.: lymphoid cells, red blood cells, and polynuclear cells containing spherules which stained with fuchsin. It is evident that Clarkson combines a description of the hemolymph glands of Robertson and the glands previously described by himself as occurring near the renal artery, the latter corresponding to those discovered by Gibbes.

In the "Journal of Anatomy and Physiology," 1897, Vincent and Harrison published a very excellent article entitled, "Hemolymph Glands of Some Vertebrates," giving a much more detailed description of these glands than previous writers, but limited almost entirely to their occurrence and structure in the lower animals. In three or four human cadavers examined they found no glands resembling those in the sheep and ox; but in a foot-note Vincent adds that in a boy of nine years he had found undoubted hemolymph glands, about fifty in number, in the mesentery and gastrocolic omentum, but had made no careful examination of them. The chief work of these observers was concerned with the glands of the ox, sheep, and rat; but the presence of similar structures was noted in the horse, dog, common fowl, and turkey. They point out further the close histological resemblance existing between the head-kidney of certain Teleostean fishes and hemolymph glands. The new points observed by Vincent and Harrison may be summed up as follows:

They found a gradual transition to exist between hemolymph glands on one side, to ordinary lymphatic glands, and, on the other hand, to the structure of spleen. No hard and fast line can be drawn marking off these structures from one another. A lymphatic gland has only to contain blood in part or the whole of its sinuses to constitute itself one of the varieties of hemolymph glands. They further point out the resemblance existing between certain accessory spleens and hemolymph glands, so that spleen, hemolymph glands, and ordinary lymphatic glands form almost a continuous series. From the presence in these glands of large quantities of

blood-pigment and phagocytes containing red blood cells they infer it to be doubtful that the hemolymph glands have anything to do with the production of red blood corpuscles, but present every appearance, in some cases at least, of taking part in the destruction of these elements.

The most recent article upon hemolymph glands appeared in the "Journal of Anatomy and Physiology," January, 1900, by W. B. Drummond. This observer made a thorough study of these organs in the sheep, ox, rat, and dog, applying numerous staining methods in the study of their finer structure. No work was done upon the human body. He confirmed the observations of Robertson, Vincent, and Harrison, and added many important points concerning the distribution and structure of the glands in the lower animals. He noted the occasional presence in them of giant-cells resembling those of the bone-marrow, and described fully the process of the destruction of red blood cells by the large mononuclear phagocytes. As to the function of these organs, he concludes that there is no sufficient evidence that they play any part in the formation of red blood corpuscles. He was unable to find any nucleated red cells, though making especial search for them. On the other hand, he considered these glands to play a very important part in the destruction of red corpuscles and in the liberation of pigment, to a greater extent even than is the case in the spleen. He believes further that they are centres for the formation of leucocytes, and that the vascular structure of the glands is such as to favor the rapid passage of white corpuscles into the general circulation. He also points out that there is an apparent cyclical function on the part of the individual glands. He regards hemolymph glands not as modified lymphatic glands but as structures *sui generis*, differing from the former in their mode of development, distribution, and in many details in their minute anatomy. Since in many respects their structure resembles that of the spleen he thinks it very likely that some of the bodies described as accessory spleens are really hemolymph glands.

From the above it will be seen what a very small amount

of work has been done with reference to the human hemolymph glands, this being practically limited to observations of their occurrence in a small number of cases by Gibbes, Robertson, and Vincent. In the first forty-nine of my cases my investigations were confined to a careful search of the retroperitoneal region and mesentery, in the last thirty-one the thoracic, mediastinal, and cervical regions have also been studied. None of my cases can be said to have been normal; the majority were chronic cases, many of which showed various stages of anemia and cachexia. In so far, then, as a division of the appearances observed by me into histological and pathological is possible, a basis for such classification can be obtained only by separating my cases into two groups: those without marked blood changes and those showing essential morbid conditions of the blood. But as many cases of severe and fatal anemias were found showing no apparent changes in the hemolymph glands, the above division holds good only for the pathological side, since only in cases showing pathological changes in the blood were conditions found in the hemolymph glands that with certainty could be considered to be essentially pathological. In all other cases the structure of these glands is assumed to be histological, this assumption being based upon the general similarity of structure in the majority of cases, and the points of resemblance between them and the hemolymph glands in normal animals. As a result of this study the following conclusions have been reached regarding the histology of the hemolymph glands of the human body.

HISTOLOGY.—The study of the retroperitoneal lymph glands reveals a most striking variety of size, form, and structure on the part of the lymphadenoid tissue found in this region. Making the broadest classification possible, we may divide these glands into two groups: glands possessing only lymph-sinuses, ordinary lymphatic glands; and glands containing blood-sinuses, hemolymph glands. The latter may contain lymph-sinuses also; intermediate forms exist, but the presence of a blood-sinus, however small, is sufficient warrant for the classification of a gland as a hemolymph gland.

Occurrence. — Taking the presence of a sinus containing blood instead of lymph as the essential feature of a hemolymph gland, such glands are found to occur in greatest numbers in the prevertebral retroperitoneal region near the great vessels, near the adrenal and renal vessels, along the brim of the pelvis, in the root of the mesentery, but rarely extending far out into it, and still more rarely in the omentum and epiploica. They are of rare occurrence along the thoracic vertebræ and in the mediastinal tissues, occurring more frequently in the thymus region. Next to their occurrence in the retroperitoneal tissues they are found in greatest numbers in the cervical region, below and behind the lobes of the thyroid in association with the parathyroids.

They differ very much in different individuals as to their location, number, and size, seldom occurring in exactly similar manner. They are more numerous in early middle life than in old age, becoming atrophic in late years. As my cases have been almost entirely adults, I cannot say anything of their relative occurrence in children. No difference has been observed in their occurrence in the sexes.

The majority of hemolymph glands lie embedded in fat tissue, and as a rule very near to the wall of some large vessel. The number and size of the blood-vessels attached to these glands is very remarkable. Some of them are supplied by a dozen or more arteries which are large in proportion to the size of the gland. The veins are also very large and numerous. The recognition of the hemolymph glands of the human body by the naked eye is very difficult and in the majority of cases impossible, because of the fact that the blood sinuses are for the greater part collapsed or emptied after death. A relatively small number may show distended sinuses; these are deep-red or bluish in color, and are easily mistaken for blood clots or hemorrhages when of small size. The smallest ones may frequently be found by holding the tissues containing them against the light and stretching the latter until the blood-sinuses in the glands are shown by red or pink streaks. Many of the larger glands show on section red points or lines corresponding to the blood-sinuses. In the

study of these organs it is therefore necessary to remove and examine all of the glands found in a given region, as only by microscopical examination can the structure of a gland be definitely determined. As the number of lymph glands in the retroperitoneal region visible to the naked eye varies between 200 to 500, and as the fat tissue all through this region contains numerous small points of lymphoid tissue which are invisible to the naked eye, it will be easily seen how difficult it is to make any estimation of the actual proportion of hemolymph glands occurring here. Though in a number of cases the entire retroperitoneal tissue has been examined both in the fresh state and microscopically, the estimation is so doubtful and the results so at variance that I do not consider myself in a position to make any definite statement concerning their number. Their relative proportion to ordinary lymphatic glands varies from 1-20 to 1-50; but this estimate is based upon incomplete observations.

Microscopically two distinct types of hemolymph glands exist, but between these there is every possible transition-form. To these types I have given the names *splenolymph gland* and *marrowlymph gland*, as indicating their structure and probable functions.

Splenolymph Glands.— This is the most frequent form, and is found chiefly in the neighborhood of the solar plexus, adrenal and renal vessels, occasionally in the omentum, mesentery, and epiploica, and in the thymus and thyroid regions. These glands are usually round, having a distinct hilum into which numerous vessels of large size enter. These are also found penetrating the capsule at numerous points. Very often the gland appears to be surrounded by a venous network. At times these glands may be recognized at autopsy by a resemblance to spleen tissue, so that they may be regarded as accessory spleens. At other times they can be identified by the red points and streaks seen on cross-section; but not infrequently they cannot be distinguished from ordinary lymph glands. Their consistency is as a rule softer than that of other lymphatic glands.

Microscopically the splenolymph glands possess a capsule

of fibrous connective tissue which is very thick in proportion to the size of the organ. It contains a varying amount of unstriated muscle and very little yellow elastic tissue. From the capsule trabeculae of similar tissues run into the gland, dividing it into irregular lobules. Between the trabeculae lies the lymphadenoid tissue. Immediately beneath the external capsule there is a small blood-sinus which sometimes extends entirely around the periphery of the gland, but more often only for portions of the way, being frequently interrupted by masses of lymphadenoid tissue which reach to the external capsule. Branches of this peripheral sinus accompany the trabeculae into the central portion of the organ, increasing in size toward the centre, where they become very large and prominent. The lumen of the peripheral sinus is traversed by a coarse reticulum in the meshes of which lie leucocytes and red blood cells. The large open central sinuses communicate with each other and with the peripheral sinus, but differ from the latter in that they possess only a scanty reticulum or none at all. In part the walls of the sinuses appear to be lined with endothelium, but in many places the blood is in direct contact with the reticulum. The circulation in these organs is therefore of the type described as sinusoidal. The nuclei of the cells of the reticulum stain much more lightly than those of the neighboring lymphoid tissue, in this respect resembling the reticulum of the lymph-sinuses in lymphatic glands. The number and size as well as the general arrangement of the blood-sinuses vary greatly, so that scarcely any two glands resemble each other in these respects.

The lymphoid tissue lying between the sinuses resembles that of an ordinary lymph gland. It varies very much in amount, sometimes forming a mere network between the sinuses, or in other cases forming the chief part of the gland. Usually the greater mass of lymphoid tissue is toward the periphery forming the inner border of the peripheral sinus, but frequently extending to the capsule, breaking up the peripheral sinus into small sections that run for a short distance only. Very often round collections of lymphoid cells are

seen, resembling splenic follicles. They occur more frequently at the periphery where they may be wholly or partly surrounded by blood sinus; but they are also found in the central portion of the gland. Serial sections show that they are almost perfectly round. In the majority of cases they possess no definite arterial relations as in the case of the splenic follicles; but occasionally a small capillary is found which under some conditions becomes gradually converted into a small arteriole with thick walls. The resemblance in these cases to the spleen is very close.

The reticulum of the lymphoid tissue appears to be like that of lymphadenoid tissue in general. The cells lying in the meshes are for the greater part small lymphocytes. These vary much with respect to relative size and staining power of nucleus, and relative amount of protoplasm. Mitotic figures are not rare. Next to the small lymphocyte the large mononuclear cell is the most common form present in the lymphoid tissue. These also vary much in size, form, and staining power. Transitional and polymorphonuclear leucocytes are also found. A small number of mononuclear eosinophiles is usually present; mast-cells are very rare. Red blood cells lie free in the meshes of the reticulum. The small blood-vessels and capillaries in the reticulum are usually filled with red cells and leucocytes, the large mononuclear form appearing to predominate. Throughout the reticulum there is usually present a varying amount of blood-pigment, partly free and partly contained within mononuclear phagocytes. Red cells in various stages of disintegration are also found in these cells. Scattered areas of a hyaline substance which stains pink with eosin, red with fuchsin, and blue with Mallory's reticulum stain are seen throughout the lymphoid tissue, more numerous near the periphery of the gland. Small hyaline, highly-refractile spherules of varying size, usually about of the diameter of a red cell, are frequently seen in small groups lying free in the reticular meshes, and also in the mononuclear phagocytes. These stain intensely with eosin and fuchsin, retaining the latter in Mallory's reticulum stain. These hyaline bodies are evidently the products

of the disintegration of red cells, as all stages of their formation can be seen. They may contain iron, especially those found in the phagocytes, the reaction being absent in many of the free bodies. In some cases these spherules can be seen partly extruded from the phagocyte.

The central blood-sinuses form the most striking features of the splenolymph glands. Though usually wholly or partly emptied they remain dilated as a rule. The scanty reticulum extends but for a slight distance into the lumen of the larger sinuses, rarely across it, except in the smaller ones. Red blood cells lie in the meshes of this reticulum and along the sides of the sinuses; here numerous large mononuclear phagocytes packed full of red cells and blood-pigment are also found. The exact manner of circulation through these glands has not yet been worked out, but it seems probable that the vessels entering at the hilum branch toward the periphery of the gland and communicate with the peripheral sinus, this empties into the sinuses running toward the centre, these in turn into the central sinuses. The latter empty into the large veins leaving the gland at the hilum, or running obliquely through the capsule. In some cases it seems that the chief circulation through the sinuses must be venous, as many large veins enter at the hilum and through the capsule, while only one or two small arteries can be found supplying the gland.

The above description applies to the typical active splenolymph gland as seen in the majority of cases. All possible transition-forms exist between it and ordinary lymphatic glands on one hand, and the spleen on the other. A combination of lymph and blood sinuses may exist in the same gland, and the amount and arrangement of the lymphoid tissue admits of the greatest variety. Serial sections may show a gland to possess blood-sinuses in one portion, and in another only lymph-sinuses.

The chief function of the splenolymph glands appears to be hemolytic. In the active glands the destruction of the red cells takes place to an extent far exceeding that in the spleen. The process, however, varies very much in individ-

ual glands in the same body; some show it to a very great extent, while others are apparently in a resting state. The appearances suggest a cyclical function. In addition to the processes of hemolysis these glands are also leucocyte-forming organs. No evidence of the formation of red blood cells has been found in them.

Marrowlymph Glands. — The second distinct type of hemolymph gland, to which I have given the name of marrowlymph glands, is of less frequent occurrence. I have found them only in the retroperitoneal region, always in close proximity to the large vessels, vena cava, abdominal aorta, renal and adrenal vessels, and common iliacs. They are found almost constantly behind the aorta, or between it and the vena cava. These glands are flattened and very long in proportion to their breadth, their greatest dimension lying parallel to the axis of the neighboring vessel. They vary greatly in size, but are sometimes very large, four to five centimetres in length. They are white or pinkish in color, with fine red lines corresponding to the blood-sinuses, and homogeneous on section. Their consistency is very soft.

On microscopical examination they are found to possess a thin external capsule which contains very little unstriated muscle. From the capsule delicate trabeculae run into the gland. Just beneath the capsule there is a blood-sinus which usually runs entirely around the periphery. From this branching sinuses run toward the central portion of the gland accompanying the trabeculae. These central sinuses as well as the peripheral one are filled with a coarse reticulum through the meshes of which the red blood cells circulate. Between the sinuses lies the lymphoid tissue arranged in irregular cords and masses. In the pure type of this variety no collections of lymphoid cells resembling follicles are seen. Numerous fat cells are present throughout the gland. The course of the blood sinuses between the masses of lymphoid tissue is plainly shown by the lighter staining nuclei of the cells of the reticulum of the sinus, and by the red cells present. The sinuses are not dilated as in the splenolymph glands. There may or may not be a distinct hilum to these

glands, and the number of blood-vessels supplying them is not so great as in the case of the splenolymph glands.

The reticulum of the lymphoid tissue is more delicate, and contains more cells. These present a greater variety than in the splenolymph glands. Mononuclear eosinophiles are more numerous, and multinuclear cells as well as large mononuclear forms with deeply-staining knobbed nuclei are also found. Occasionally cells of the type of bone-marrow giant-cells are seen, but these are rare under normal conditions. There is much greater diversity of form and staining power in the small lymphocytes and large mononuclear hyaline cells. No nucleated reds have been found under normal conditions. Phagocytes containing red cells, pigment, fuchsinophile bodies, and leucocytes are also present, but in much smaller numbers than in the splenolymph glands. Deposits of hyaline material are of frequent occurrence. Red blood cells are found scattered throughout the reticulum of the lymphoid tissue in large numbers. There is also a great variety of cells in the reticulum of the blood-sinuses; many large mononuclear and multinuclear cells with pale-staining nuclei being present.

Combination-forms of spleno and marrow lymph glands exist as well as transition-forms between the two, and also between marrowlymph glands and ordinary lymph glands. The function of the marrowlymph glands under ordinary conditions is not so clear as in the case of the splenolymph variety. The part which they play in hemolysis is evidently more limited than in the case of the latter. They are evidently also leucocyte-forming organs. The presence of giant-cells and many mononuclear eosinophiles suggests the bone-marrow and the formation of red cells. Though these glands undoubtedly form red blood cells under certain pathological conditions, I have not yet found any absolute evidence that they do so under normal conditions. Rather, they appear, in so far as this function is concerned, to be in a resting state, or to perform it but to a very slight degree. The structure of the gland certainly points to some important function in connection with the blood. In old age the mar-

row glands become very atrophic, their blood-sinuses are obliterated, large deposits of hyaline occur, and finally they cannot be distinguished from atrophic lymphatic glands.

In the study of the retroperitoneal glands I have constantly found in the fat tissue of this region lymphadenoid structures too small to be seen by the naked eye, or to be recognized as lymph glands. These occur in a most surprising variety of form, such as small points of lymphoid tissue with a very thick capsule and peripheral blood sinus; broad and thin sheets of very irregular form possessing no capsule, and occasionally containing nodes resembling splenic follicles; cords of lymphoid tissue with capsule one to two millimetres in diameter running parallel to vessels for several centimetres; irregular masses of lymphoid tissue without capsule or sinus surrounding blood-vessels, etc. The significance of these forms is unknown, but as all possible transition-forms exist between these and definite glands, I look upon them as being of the nature of resting lymphadenoid structures which under certain pathological conditions may play a compensatory rôle for either the spleen or bone-marrow. That they are not atrophic I think is shown by the absence of hyaline, connective tissue increase, etc. Further, the appearances often suggest a transformation of adipose tissue into lymphoid tissue, and the possibility of a physiological rotation of the two forms of tissue.

PATHOLOGY. — Various pathological conditions, such as inflammation, congestion, carcinoma metastases, tuberculosis, etc., were found affecting these glands in common with ordinary lymphatic glands. In a limited group of cases, however, very striking changes were found that must be looked upon as being specific in character. Very briefly these were as follows:

Pyemia. — In one case of thrombo-phlebitis purulenta of both femorals, iliacs, and ascending vena cava, the marrow glands were found enlarged and congested. On microscopical examination there were evidences of an increased proliferative activity in the lymphocytes, as shown by numerous dividing cells. Numerous mononuclear eosinophiles were

present throughout the lymphoid reticulum and also in the reticulum of the blood-sinuses. Nucleated red blood cells were present, both normoblasts and larger cells resembling those in the bone-marrow. Multinucleated and mononuclear cells of large size were numerous, a few resembling the bone-marrow giant-cells. Large numbers of phagocytes were present in the reticulum of the blood-sinuses, and throughout the gland numerous pigment granules and fuchsinophile bodies were seen. An unusually large amount of hyaline substance was also present. From these findings it seems safe to conclude that in this case the marrow glands were centres of both leucocyte and red cell formation, as well as showing an increased destruction of red cells. The splenolymph glands in this case showed increased hemolysis.

Anemia. — In all of the cases of marked anemia examined, either the splenolymph or the marrow glands showed changes of greater or less extent. These changes varied with the nature of the anemia.

Secondary Cachectic Anemia. — In a large number of severe cachectic anemias both marrow and splenolymph glands showed increased hemolysis, but no evidences of new formation of red cells were found.

Pernicious Anemia. — In five cases of fatal anemia without other pathological conditions, both spleno and marrow lymph glands showed increased pigmentation without evidences of new formation of red cells. In these cases no evidences of increased activity were found in the bone-marrow.

Anemia Gravis with Hemorrhages. — In one case of fatal anemia associated with repeated severe attacks of epistaxis, hematemesis, and bloody stools, the only marked changes found on autopsy were in the retroperitoneal lymph glands. These were enormously enlarged, forming an almost continuous double row along the abdominal aorta, and diverging below along the brim of the pelvis. Each gland was three to four centimetres in length, and one to two centimetres in thickness. They were almost cylindrical, somewhat flattened above, and were dark-red in color, almost black. On

section the blood flowed freely from the very large dilated vessels. The glands to the left of the aorta were somewhat larger than those between it and the vena cava. On microscopical examination an extensive hyperplasia of the lymphoid tissue was found extending beyond the original capsule of the gland into the surrounding fat tissue. The veins and larger sinuses of the glands were enormously dilated; the majority of the blood-sinuses were obliterated by the hyperplasia of lymphoid tissue. Cords of lymphoid cells extended into the surrounding fat tissue on all sides. The presence of small isolated areas of lymphoid tissue in the fat suggests the possibility of the fat being changed into lymphadenoid tissue. The general appearances are also suggestive of lymphosarcoma. On the other hand, I am inclined to look upon the process as being of the nature of a compensation for the bone-marrow. Numerous mononuclear eosinophiles, nucleated red cells, and occasional giant cells are found throughout the reticulum of the lymphoid tissue. A few normoblasts showing mitosis were found, and mitotic figures in the lymphocytes are frequent. The blood of this case contained very few normoblasts and showed an increase of small lymphocytes. The other lymph glands of the body were prominent, probably slightly enlarged, but showed no changes resembling those in the retro-peritoneal hemolymph glands. There was a marked osteoporosis of the long bones, the medullary canal containing many cysts filled with blood. No new formation of lymphoid marrow was found.

Fatal Anemia following Epistaxis.—In a case of fatal anemia following epistaxis, the only lymph glands showing change were those of the retroperitoneal region, especially those in the neighborhood of the solar plexus. Microscopically these glands presented an extraordinary appearance, in all respects corresponding to that of lymphoid marrow. Throughout the reticulum are numerous giant-cells of all varieties, resembling those of the marrow, large numbers of mononuclear eosinophiles, nucleated reds, both large and small, large mononuclear leucocytes corresponding to mye-

locytes, and all possible varieties of transitional forms of leucocytes. With tri-acid staining the number of different cell-forms is bewildering, and constitutes a subject much too broad to be entered upon here. All of the forms found in marrow and many others not found there are present. The giant-cells appear to arise from the endothelial cells of the reticulum; and in many cases they appear to have processes which are continuous with those of the reticulum and stain similarly. Between the small lymphocyte, hyaline mononuclear and nucleated red cells all stages of transition may be traced, but as to the mode of origin of the latter I am not yet prepared to offer a final opinion, but hope that the study of this case may throw some important light upon this problem. The bone-marrow showed scattered areas of lymphoid marrow, and both liver and spleen showed changes suggesting a return to a fetal mode of blood formation. The remaining lymph glands showed no enlargement, and on microscopical examination presented an appearance of fibroid hyperplasia. Numerous nucleated red cells were present in the blood.

Splenic Anemia.—In one case of splenomegaly with severe anemia, the patient dying after splenectomy, the adipose tissue of the mesentery and retroperitoneal region showed countless points and streaks of lymphoid tissue. These are usually found surrounding a small arteriole, which shows a much thickened and proliferating wall; in some cases the vessel is completely obliterated by the proliferation of its intima. The tissue blocking the lumen has in many cases undergone a hyaline change, and in some instances calcification has taken place. Occasionally the lymphoid cells are grouped around the arteriole after the manner of a splenic follicle. The small lymphadenoid collections possess a reticulum and individual blood supply. They cannot be regarded as simple inflammatory collections of leucocytes. They resemble very much the changes found in the omentum by Tizzoni in his experimental work on the regeneration of the spleen after complete removal of that organ. I am inclined to interpret the findings in my case as significant of

splenic compensation. This view is further borne out by the fact that in this case a number of glands resembling accessory spleens were found in the gastro-splenic omentum and in the retroperitoneal tissues near the pancreas. I look upon these as compensating splenolymph glands.

Leukemia. — In three autopsy cases of leukemia the retroperitoneal glands were found to show specific changes in but one case (lieno-myelogenous leukemia). The gross appearances in this case were similar to those in the case of pernicious anemia associated with hemorrhage, except in regard to the color of the enlarged glands. As in the other case, a double row of large, oval, flattened glands extended along both sides of the abdominal vertebral column, in close relations with aorta and vena cava, diverging below along the common iliacs. About forty glands in all showing specific changes were found. The other lymph-glands of the body showed very slight enlargement. The enlarged retroperitoneal glands were very pale pinkish yellow in color, and of soft crumbling consistency. They were supplied by numerous blood-vessels of very large size. On microscopical examination they were found to possess a very delicate connective tissue capsule, from which delicate trabeculæ passed into the gland dividing it up into lobules. Accompanying the trabeculæ were blood-sinuses whose reticulum showed great hyperplasia, its meshes being almost filled with giant-cells like those of the marrow — mononuclear eosinophiles, myelocytes, and an almost infinite variety of leucocytes. Nucleated red cells were present in large numbers. The course of the sinuses is strikingly outlined by the great numbers of giant cells found in their reticulum. These occur also in great numbers in the reticulum of the lymphoid tissue. In a low-power view of sections of these glands there is seen in the central portion of each lobule a mass of cells whose nuclei stain very deeply; around these areas there is a broad zone of cells with nuclei staining very lightly; outside of this zone is the blood-sinus with its reticulum filled with giant cells. The central deeply-staining areas are made up of lymphocytes chiefly, the lighter zone around these chiefly of large

mononuclears. With the tri-acid stain an infinite variety of cells is shown as in the fatal case of anemia following epistaxis. In a general way the changes in the glands in this case and that one are identical; in both the marrowlymph glands have become changed into structures exactly resembling lymphoid marrow. In this case as in that one also the actual bone-marrow showed but little lymphoid hyperplasia. From this it may be inferred that in cases of diminished energy on the part of the blood-forming function of the bone-marrow the marrow glands take up this function to an extraordinary degree.

Summary. — Making a very brief summary of both histological and pathological appearances noted in my investigation:

Lymph glands with blood-sinuses are constantly present in the human body. Two types may be recognized. To these I have applied the terms splenolymph and marrowlymph glands; but between these transition forms exist, as well as between these glands and the spleen on the one hand, and ordinary lymph glands on the other. Under normal conditions the hemolymph glands are most probably concerned chiefly in hemolysis and leucocyte formation, and play but little part if any in the formation of red blood cells. In diseases in which the blood shows marked changes, specific conditions are found in these glands of such a nature as to place beyond doubt their blood-forming function.

Further, the study of the retroperitoneal tissues makes it very probable that the lymphadenoid structures present there are not stationary, but are constantly undergoing progressive and retrogressive changes, possibly of a cyclical nature. The intimate relationship existing between adipose tissue and lymphadenoid tissues is here strikingly shown; and the probable metaplasia of the former into the latter, as in the case of splenic anemia, confirms in a very important way the observations of Bayer, Tizzoni, and others. The close relations between spleen, lymph glands, and bone-marrow is shown by the power of the hemolymph glands to take on the structure of either spleen or marrow, and to compensate for these organs when their function is abridged by disease.

Many interesting problems are encountered in the study of these glands: the fate of blood-pigment, the formation of fuchsinophile bodies, and of the hyaline substance found in the reticulum, the development of marrow-like giant cells from the reticulum both of the blood-sinuses and lymphoid tissue and probably also from the endothelial cells lining the sinuses, the relation of these and mononuclear eosinophiles to the formation of red blood cells, the possible rapid formation and passage of leucocytes into the circulation in leucocytosis, and finally the development of nucleated red cells themselves. In regard to the latter point transition-forms apparently exist between small lymphocytes and erythroblasts and also between hyaline mononuclear leucocytes and nucleated red cells, so that the views of Löwit and Howell appear to be confirmed.

In conclusion, it may be said that the study of these glands opens up many new and important lines of investigation with regard to the solution of the problems relating to blood-formation and pathological conditions of the blood and blood-forming organs, as seen in the various forms of anemia, leukemia, etc. The field of hemolymph gland histology and pathology, almost entirely neglected in the past, promises to be a fertile one yielding rich results to such investigations.

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THE RELATION BETWEEN PHYSIQUE AND MENTAL WORK.

(Second Paper.)

HENRY G. BEYER.

During the winter of 1899 I engaged in some studies regarding the relation existing between certain physical dimensions, and mental examination-marks obtained from some eighty-five navy yard apprentices, varying in age from fifteen to seventeen years. The results of these studies, which were published in February, 1900, in Vol. IV., No. 6, of this Journal (1), were of such importance as to make it seem desirable to extend the observations on a large number of school children, if possible, with the view of testing the correctness of the conclusions that were reached at that time, but from a comparatively speaking small number of boys. The work seemed especially promising for the reason that we were already in the possession of growth-tables of the children of Massachusetts (2), and because the existence of these tables permitted us to employ the same method of investigation as had been employed in similar work during the preceding year.

This method, as some of you may perhaps remember, consisted in attaching to each boy, instead of the absolute height, weight, etc., the percentile rank or value to which these measurements would correspond, and which is easily found on the tables mentioned, before making the comparison between the physical and mental marks. The method seems to be especially valuable for the reason that it introduces a certain very desirable element of homogeneity into the comparison between the physical and mental grades of children. Both stand for the fact that a child has attained so many points out of a possible one hundred, in both its physical and mental examinations. The method, therefore, puts both physical and mental examination-marks on a percentile basis, and hence must lead to a comparison from which, to say the least, results more striking may be expected than those obtained by former methods.

An opportunity for obtaining a number of measurements of children varying from ten to thirteen years of age, and belonging to the schools of Cambridge, Mass., was afforded me last year through the kind intervention of Prof. D. A. Sargent, who not only obtained for me the necessary permission from the school authorities of Cambridge, but also allowed me to engage the services of some of his advanced pupils in anthropometry to do the necessary weighing and measuring. My thanks are therefore due Professor Sargent for both these concessions.

Desirable as it would have been to obtain the chest circumference in addition to height and weight, the circumstances did not seem favorable enough, and thus it happened that our observations must be limited to height and weight alone. In working up the material, as will be seen in the tables, the boys and girls are treated separately. The cards belonging to each were classified, first, according to the age, as calculated from the nearest birthday, and second, according to the different school grades through which the children were found distributed. This having been done, the absolute height and weight noted on each card were converted into percentile grade values, in accordance with the growth-tables of H. P. Bowditch, and the various values added together, their sums averaged and tabulated. The results are exhibited on Tables I and II.

TABLE I.

AGE NEAREST BIRTHDAY. Years.	Grade.	Number Examined in Each Grade.	PERCENTILE RANK. Boys.		AVERAGES.	
			Height (in.).	Weight (lbs.).	Height (in.).	Weight (lbs.).
10	3	10	53.5	39.0	61.05	55.00
	4	50	50.1	46.1		
	5	54	62.9	54.6		
	6	34	74.7	67.2		
	7	7	77.8	68.5		
	9	1	100.0	100.0		
		— 156				
11	2	1	20.0	20.0	53.20	50.10
	3	16	36.5	38.1		
	4	101	45.5	44.9		
	5	145	55.0	50.0		
	6	128	56.9	54.3		
	7	36	58.4	53.3		
	8	7	66.6	54.2		
	9	2	90.0	95.0		
		— 436				
12	2	1	20.0	20.0	50.60	48.00
	3	14	30.7	38.2		
	4	65	39.6	44.5		
	5	104	41.8	41.1		
	6	130	55.1	49.5		
	7	94	55.2	49.0		
	8	30	69.0	58.6		
	9	15	79.0	74.0		
	10	1	20.0	80.0		
		— 454				
13	3	5	22.0	24.0	44.00	45.00
	4	24	33.5	34.5		
	5	60	41.2	41.5		
	6	73	41.7	41.1		
	7	71	50.1	46.5		
	8	49	60.2	56.0		
	9	24	56.0	46.2		
	10	9	64.4	58.3		
	11	2	85.0	65.0		
		— 317				
		Total, 1,363				

TABLE II.

AGE NEAREST BIRTHDAY.	Grade.	Number Examined in Each Grade.	PERCENTILE RANK.		AVERAGES.	
			GIRLS.		Height (in.).	Weight (lbs.).
Years.			Height (in.).	Weight (lbs.).		
10	4	58	55.0	59.0	73.6	74.1
	5	47	60.5	72.5		
	6	48	77.6	71.4		
	7	5	85.0	68.0		
	8	1	90.0	100.0		
		— 159				
11	3	22	34.7	39.0	53.2	54.8
	4	113	37.4	40.5		
	5	132	44.4	46.0		
	6	97	57.1	57.3		
	7	60	71.0	67.0		
	8	10	75.0	79.0		
	— 434					
12	4	60	40.2	38.1	51.4	50.2
	5	108	44.7	44.4		
	6	128	44.5	41.0		
	7	117	49.2	49.2		
	8	39	58.9	57.9		
	9	13	71.1	71.1		
	— 465					
13	4	28	31.6	34.4	43.5	44.0
	5	45	32.8	37.6		
	6	86	40.3	40.4		
	7	82	46.3	47.6		
	8	59	48.1	44.2		
	9	31	62.4	60.0		
	— 331					
		Total, 1,389				

These tables show an almost unbroken increase in percentile rank of both height and weight among children of the same age, as we follow the different columns from above downward or from the lower to the higher school grade.

This fact is even more strikingly seen when comparisons are made between individual examination marks instead of whole grades and percentile grade marks, providing, of course, that children of the same age are used in such comparisons. This, however, could not be carried out without unduly increasing the number of tables that would become necessary in order to exhibit the results.

It seems, then, a clearly established fact that the amount and quality of intellectual work done by children is directly proportional to the percentile rank in their physique. So far as our own observations extend, this is true of children from ten to seventeen years of age. Whether this is equally true for adults is a question still awaiting further investigation.

Since the publication of my first paper, two articles on similar subjects have come to my notice. One is by Prof. William W. Hastings (3), who studied the heights and weights, in their relations to the school grades, of some Nebraska children aged eight to eleven years. The other is by Dr. W. S. Christopher (4), whose opportunities gave him a wide scope, for he included in his observations height, weight, strength of grip, ergographic tests for endurance, vital capacity, and hearing.

The conclusions of both Professor Hastings and Dr. Christopher are, in the leading points, identical with those I expressed in a former paper. Christopher says, on page 25: "It is clear from the foregoing charts and tables that on the average those pupils who made great intellectual advancement on the whole are taller, heavier, stronger, possessed of greater endurance, of larger breathing capacity, than those who have made less advancement." He also makes a note of an interesting fact observed by myself several times in connection with this work. He says: "In every school there are a few pupils who are small in stature and light in weight,

and yet exceedingly bright in their school work," and he considers these as constituting a class by themselves and deserving special consideration. An interesting example of this class may be seen on Table I., under twelve years. We will find under that head one boy in the second grade and one in the tenth grade, both of the same percentile grade in height, namely, twenty. When, however, we look at the column of weights we find that the tenth grade boy belongs to the eightieth percentile grade, while the second grade boy belongs to the twentieth percentile grade. This instance would perhaps, again, serve to emphasize the importance of weight at that age, to enable a child to keep up with the procession in school.

In the two columns of averages on both Tables I. and II. we will notice a sort of paradoxical decrease in the average percentile rank for both height and weight, as we follow them from the tenth to the thirteenth year, or from above downward. This decrease in the average percentile rank noted as we proceed from the younger to the older children is very significant and can, so far as I can see, be explained by the fact that the numerical proportion of the exceptionally tall, heavy, and bright boys and girls to the mediocre ones becomes less great as years go on, brought about, apparently, through the influence of mental training exerted upon the latter class of children. For when we calculate the averages of the different grades regardless of age, we again obtain an increasing series of physical rank as we proceed from the lower to the higher school grades, the same as when the classification was made according to age, as may be seen in the following Table III.:

TABLE III.

Grades. All Ages.	PERCENTILE RANK.	
	Height.	Weight.
3	35.67	34.82
4	42.17	42.50
5	50.22	46.80
6	57.10	53.00
7	60.37	54.32
8
9	81.25	78.86

Another possible explanation for this decrease in average might perhaps be found in that the bright and tall boys pass on to higher grades so quickly as to leave the lower classes with a lower and steadily decreasing average, from year to year, so far as physique is concerned.

However that may be, the principal conclusion arrived at in one of my former papers, namely, that physical and mental qualifications are directly proportional and generally found associated in growing school children, has again been found to be true. The great ease, moreover, with which it can be demonstrated in any number of children, whether large or small, would certainly predispose one to assume that a causal relationship exists between physical and mental qualifications. Added to this the further fact that we can increase the height, weight, lung capacity, and strength through a carefully graded and scientifically supervised system of exercises, over and above that amount which would result without such exercise, the whole subject of physical training assumes at once an enormous importance, stands at once in a truer and clearer light, and on a much firmer and much more solid foundation than ever before.

Before, however, we pronounce the existence of a relationship between physique and mental work as one of cause and

effect, let us look at and examine another side of the question. So far we only have shown this relationship to exist in growing children, and we therefore do not know whether it holds true for adults. Nor have we yet even thought of studying or investigating the possible influence of mental training upon the physique of our children. We have generally assumed that mental training, especially when it is overdone, is inhibitory to sound physical development. Might it not also be true that physical training, when it is overdone, might dwarf mental development? Could it perhaps be possible that the relation between physical and mental development is one of reciprocity? That the careful and proper development by the training of one must exercise a favorable reflex influence upon the development of the other? Have we anything that would even suggest the possibility of mental training such as our children get in schools, influencing favorably the development and growth of their bodies?

While thinking about this subject, it occurred to me that one of the means of approaching the problem with a chance of getting some light on it would be to compare the growth curves between boys who went through the high school and into college, and those who did not, beginning after both left the grammar schools, at the same time selecting a class of boys in whom no other essential differences as regards environment and other hygienic conditions exist; in other words, boys in whom the superior mental training which they get in the higher schools can be said to constitute the chief, if not the only, difference influencing their lives and growth.

An approach to such a condition may be found in the difference in the training of naval cadets on the one hand, and naval apprentices on the other. Both classes of boys start about the same age; their work on board ship as well as their drills on shore are almost identical; the food which they get has about the same value in caloric, the difference being that the cadets are served better than the apprentices (5); both get at least eight hours' sleep; the cadets do about the same amount of work with their hands as do the apprentices; in fact, we have here the rather rare opportunity of comparing

conditions of life in which the superior mental training received by the cadets at the naval academy may be said to constitute the chief, if not the only, difference. Consequently their respective growth curves, when compared to one another, ought to give some very valuable information with regard to this point.

The necessary material for such curves was found, partly in the growth tables published by me in 1895 (6), partly in tables not yet published, and compiled from the physical examination records of a large number of naval apprentices and landsmen for training.

TABLE IV.

Mean Values, Derived from 4,541 Cadets and 3,445 Men and Boys, Compared.

AGE.	HEIGHT (in.).		WEIGHT (lbs.).		CHEST CIRCUM. (in.)	
	Cadets.	Men.	Cadets.	Men.	Cadets.	Men.
15	64.29	63.37	108.50	109.00	29.95	30.07
16	65.80	64.01	116.90	114.42	31.10	30.40
17	67.00	64.87	124.80	122.60	31.89	31.34
18	67.63	65.43	131.80	124.94	32.68	31.80
19	67.65	65.68	137.00	128.45	33.25	32.00
20	68.25	65.84	138.50	133.90	33.58	32.50
21	68.21	66.10	138.90	134.90	33.65	33.14
22	68.35	66.31	138.70	140.08	33.77	33.62
23	68.52	66.45	138.30	140.85	33.87	34.00

The adjoining Table IV. exhibits the differences in the mean height, weight, and chest circumference between the two classes of boys. On examining the several columns in this table, we will notice, so far as weight and chest circumference are concerned, the apprentices have a slight advantage over the cadets, beginning, as they do, with a somewhat higher mean in both. As regards height, the cadets would seem to have a more decided advantage over the apprentices,

beginning with a difference in their favor of a little less than one inch.

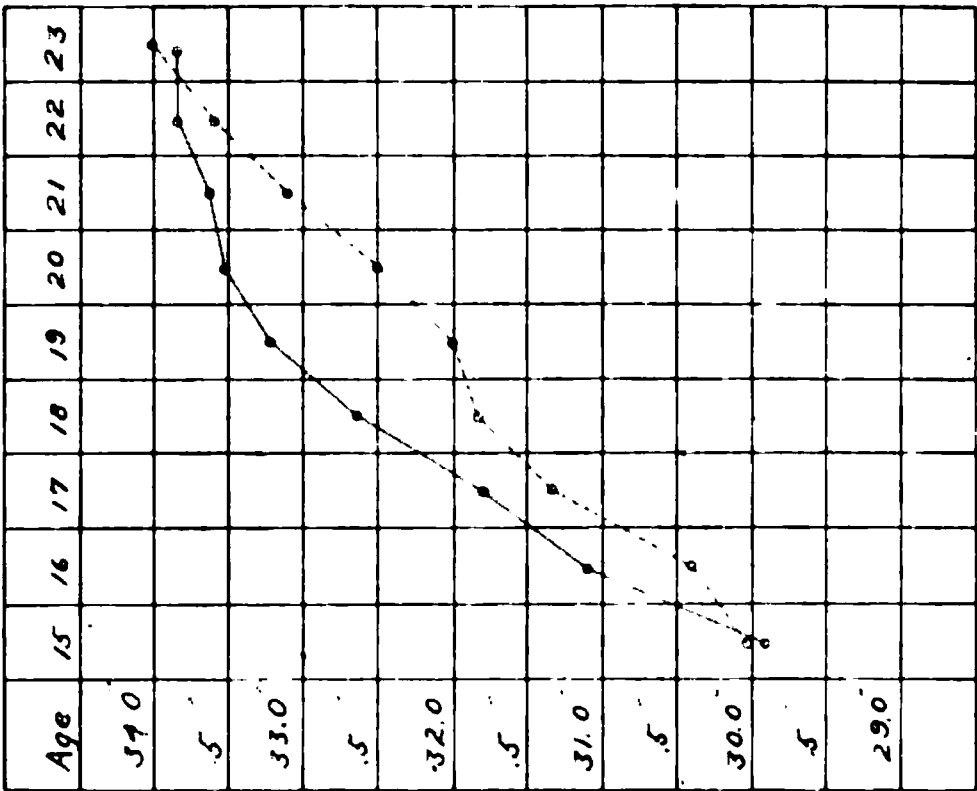
When we follow them from the very beginning of their respective periods of training — that is, from their fifteenth year on upwards — we find that the cadets rapidly gain over the apprentices and pass ahead of them in all three dimensions until they arrive at the eighteenth and nineteenth year. Here a marked change occurs. The apprentices slowly gain on the cadets in weight and chest circumference and actually pass them at the twenty-third year, while in height the cadets keep permanently in the lead and finish at the twenty-third year with a difference in their favor of two inches. These relations are seen more strikingly represented in the adjoining three charts.

From the facts brought out in the foregoing study we may conclude: (1) That a high percentile rank in height, weight, and chest circumference, in growing children, is nearly always found associated with a superior grade of mental work, as that is determined ordinarily in our schools. (2) That the relationship between physique and mental ability is such that the training of the one will indirectly and favorably influence the growth and development of the other, when the training of either is kept within physiological limits.

LITERATURE.

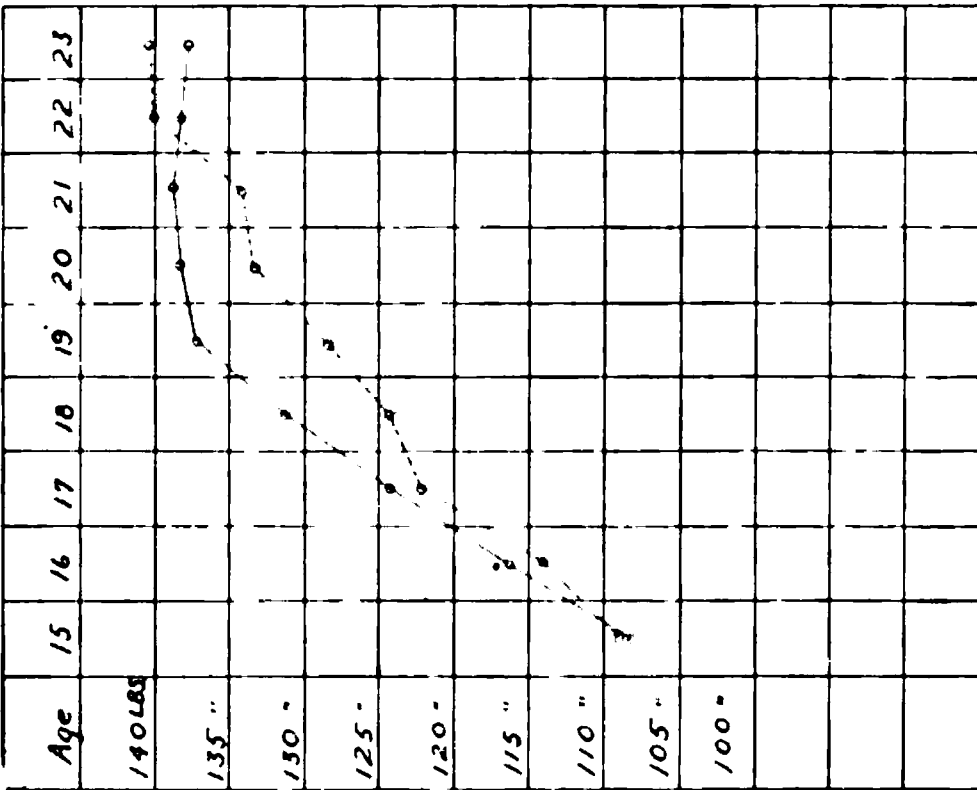
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III Mean Chest Cir Compared.



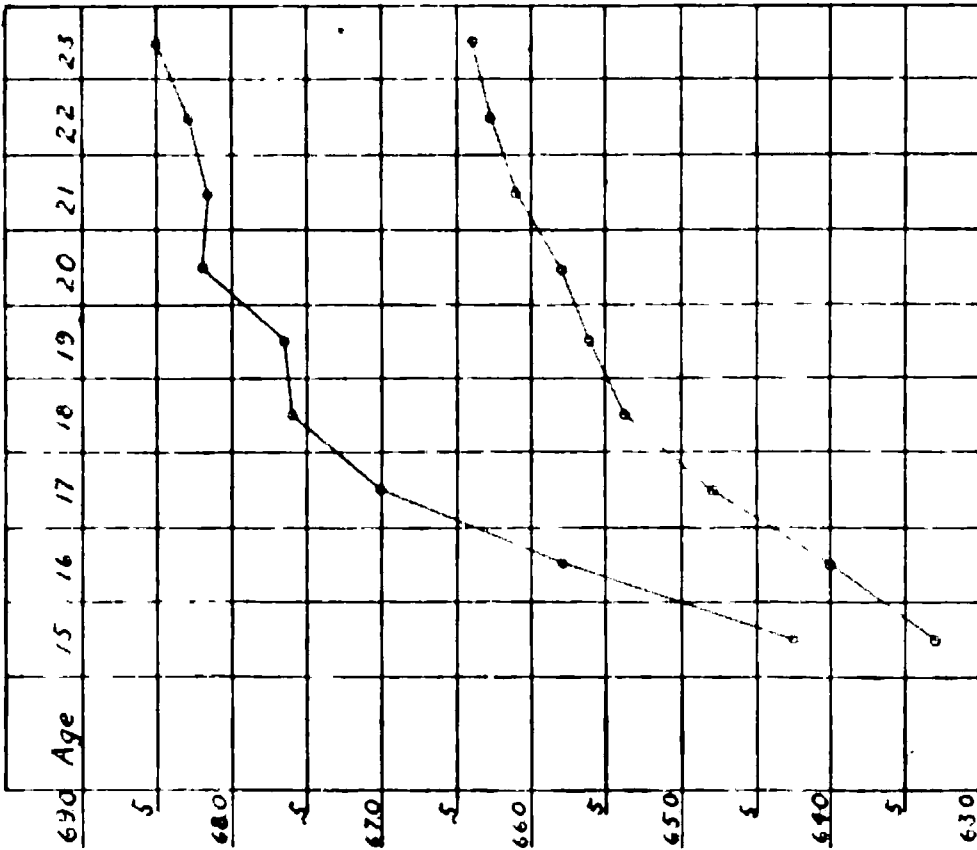
Upper line: Cadets.
Broken line: Men.

II Mean Weights Compared.



Upper line: Cadets.
Broken line: Men.

I Mean Heights Compared.



Upper line: Cadets.
Lower line: Men.

TYPHOID CHOLECYSTITIS, WITH OBSERVATIONS UPON
GALL-STONE FORMATION.

JOSEPH H. PRATT.

*(From the Pathological Laboratory of the Boston City Hospital.)**(Abstract.)*

During the past four years at the Boston City Hospital cultures from the gall-bladder have been made at the autopsy in thirty cases of typhoid fever. In twenty-one the bacillus typhosus was obtained. In one of these cases there was a catarrhal cholecystitis; in all the others the bile and gall-bladder appeared normal. In five of the nine negative cases the bacillus typhosus was not found in any of the organs.

As the gall-bladder in typhoid fever usually contains the typhoid bacillus, and as inflammation of the gall-bladder is relatively rare, some factor other than the presence of the typhoid bacillus must be necessary to produce cholecystitis.

The typhoid bacillus may remain in the gall-bladder after it has disappeared from the other organs. In two cases I found it in the gall-bladder, while cultures from the heart's blood, spleen, liver, and kidney were negative.

The typhoid bacillus probably infects the bile through the blood. It is practically always found in pure culture in the gall-bladder. In the eleven cases of invasion of the gall-bladder by the typhoid bacillus, of which I have the full bacteriological notes, it was found in pure culture in every instance. If infection took place through the biliary passages we should expect to have a mixed infection with the bacillus coli or the streptococcus, as Miyaki has shown that these bacteria are generally present in the lower portion of the ductus choledochus.

Typhoid septicæmia is no longer regarded as an extremely rare condition. We have obtained the bacillus typhosus, at the autopsy, from the heart's blood in three out of twelve cases. I isolated the microörganism in one case from the heart's blood, the spleen, the liver, the kidney, a mesenteric

lymph node, the gall-bladder, the urinary bladder, the right middle ear, and the bone-marrow.

If we regard every case of invasion of the gall-bladder by the typhoid bacillus, without symptoms and without pathological changes, as a case of cholecystitis, then, as we have shown, every case of typhoid is a case of cholecystitis. This is confusing and unreasonable. We should limit the term "cholecystitis" to those cases in which there is clinical or pathological evidence of inflammation of the gall-bladder.

The theory advanced by Naunyn in 1891, that gall-stones are due to a catarrhal inflammation of the gall-bladder induced by microorganisms, has been generally adopted. It is supported by experimental and bacteriological evidence. The bacillus coli and the bacillus typhosus are the bacteria usually associated with cholelithiasis. Mignon believes that the formation of stones ceases with the death of the bacteria. Old stones are sterile.

The cases of cholecystitis caused by the bacillus typhosus can be divided into two classes: (1) Cholecystitis secondary to typhoid enteritis; (2) cholecystitis due to a primary infection of the gall-bladder.

Since Dr. Mason published his report in 1897, five cases of cholecystitis due to the typhoid bacillus have been studied at the Boston City Hospital. Three of these occurred during typhoid fever.

CASE I. — Patient died in the fifth week of typhoid fever. There were no symptoms referable to the gall-bladder. The bile contained great numbers of minute shreds. Microscopical examination revealed large masses of desquamated epithelium and great clumps of bacilli morphologically identical with the bacillus typhosus.

Bacteriological Examination.—A bacillus varying in length decolorized by Gram; no gas production in a Smith fermentation tube containing one per cent. glucose bouillon; motile in twenty-four-hour bouillon cultures. The microorganism was agglutinated by the blood of a typhoid patient diluted 1:30. Blood was collected at the autopsy, sealed in a glass tube, and tested seven days later. It agglutinated the bacil-

lus obtained from the gall-bladder in dilutions of 1:100 and 1:200; no reaction 1:500. It agglutinated a culture of the stock typhoid bacillus in the same dilutions. Diagnosis: bacillus typhosus.

CASE II. — During the fourth week of typhoid fever, cholecystostomy was performed in a case of suspected cholecystitis. The gall-bladder contained dark bile and some puriform material.

Bacteriological Examination. — A cover-slip preparation from the contents of the gall-bladder showed medium-sized bacilli decolorizing by Gram's method. In cultures a pure growth of this bacillus was obtained. It has the following characteristics. No gas production in glucose agar; acidifies milk very slowly; does not coagulate milk; no indol production in glucose-free bouillon; agglutinated by the blood of a typhoid fever patient. Diagnosis: bacillus typhosus.

CASE III. — Woman, aged 36. No history of previous illness. During the third week of typhoid fever symptoms suggestive of cholecystitis developed. At the operation Dr. Munro found the gall-bladder swollen, tense, and filled with bile and creamy pus. It also contained a number of gall-stones. The patient recovered.

Bacteriological Examination. — Seven small spherical gall-stones, one to three mm. in diameter; surface dark, brownish gray, crenated. They are friable; centres yellowish. A serum culture inoculated with the pus from the gall-bladder, and agar plates from the nuclei of two of the calculi, gave pure cultures of the typhoid bacillus. Growths from six different colonies each showed: A bacillus decolorizing by Gram's method; motile in twenty-four-hour bouillon cultures; invisible growth on potato; milk not coagulated; no gas production in glucose agar; no indol in glucose-free bouillon. Agglutinated by blood of a typhoid patient in fifteen minutes, dilution 1:25.

In this case there can be little doubt but that the typhoid bacillus was the cause of the cholelithiasis. If so, it would seem as if the calculi must have been formed within eighteen days, and it is probable that they were formed in much less

time. This is in accord with the view of Naunyn, who believes that gall-stones can be formed in a very short time.

CASE IV. — Woman, aged 43. Two attacks of biliary colic, one seven, the other six years ago. No history of typhoid or other continued fever. Symptoms of cholecystitis suddenly developed. Operation on the eighth day of illness. Gall-bladder distended with pus. Two hundred and eighteen gall-stones were removed from it.

Bacteriological Examination. — A cover-slip preparation from the gall-bladder showed polynuclear leucocytes and a few short bacilli which were decolorized by Gram's method. Culture on blood serum gave a diffuse growth of a short bacillus decolorizing by Gram, present in pure culture. It had the following characteristics: Distinctly motile; bouillon diffusely clouded; invisible growth on potato; litmus milk rendered acid, not coagulated; no indol production; no gas in glucose, lactose, or saccharose bouillon. Diagnosis: bacillus typhosus.

The gall-stones varied in size from 3.5 mm. to 1 cm.; pyramidal shaped; brownish yellow; mottled; central portion dark brown; grayish-white outer layer, marked with radiating striæ. No cultures were made from the calculi at the time of the operation. Three months later I got possession of them, and although they had been kept in a hot, dry atmosphere, I made cultures from the nuclei of ten of the gall-stones. Cultures from eight of the stones remained sterile. From the other two I obtained a meagre but pure growth of the typhoid bacillus.

The history in this case dates back seven years, so it is probable that the gall-bladder harbored the bacillus typhosus for that length of time.

CASE V. — Woman, aged 36. No history of typhoid fever. Patient admitted to the hospital with symptoms of cholecystitis. The gall-bladder was greatly enlarged and covered with flakes of fibrin. On incising the organ a large amount of greenish-yellow pus escaped. A portion of the wall of the gall-bladder was removed as it appeared to be gangrenous.

Temperature fell gradually after the operation. The patient made a good recovery.

Bacteriological Examination.—Cover-slip from external surface of gall-bladder showed an occasional polynuclear leucocyte; rather numerous bacilli. Culture on blood-serum after twenty-four hours showed a diffuse grayish-white growth of a medium-sized bacillus decolorizing by Gram. A similar bacillus was obtained in pure culture from the contents of the gall-bladder. Both had the following properties: Actively motile in twenty-four-hour bouillon cultures; milk not coagulated; no indol production; no gas produced in glucose, lactose, or saccharose bouillon. Agglutinated by blood of a typhoid fever patient 1:10; no reaction 1:25. Agglutinated by patient's own blood 1:10; no reaction 1:25. Known typhoid bacillus agglutinated by patient's own blood 1:10; no reaction 1:25. Diagnosis: bacillus typhosus.

As there were no symptoms or history of typhoid fever in these two cases they are probably instances of primary infection of the gall-bladder with the bacillus typhosus.

In 1898 Cushing reported a case similar to these, and Mitchell has recently recorded another. Hunner studied a case of cholecystitis in which he considered the bacillus typhosus had been retained within the body since an attack of typhoid fever eighteen years before. I agree with Horton-Smith, however, that the evidence in Hunner's case points rather to a local infection. If it be included we have, with the two here reported, five cases of primary infection of the gall-bladder.

SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society.

All communications should be addressed to the Editor,

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A NEW MOULD-FUNGUS AS THE CAUSE OF THREE CASES
OF SO-CALLED BLASTOMYCOSIS OR OÏDIOMYCOSIS OF
THE SKIN.

A Preliminary Report.

HOWARD T. RICKETTS,

Fellow in Cutaneous Pathology, Rush Medical College.

(From the Pathological Laboratory of Rush Medical College.)

The following cases of oïdiomycosis (blastomycetic dermatitis, Gilchrist) of the skin have been studied recently, and a mould fungus isolated from each.

Case I.—A German, 73 years old, a laborer, and of negative family history, came to my dispensary clinic at Rush Medical College in October, 1900.

In February, 1898, a pimple appeared on the scalp above the lobe of the left ear. It became a pustule which crusted, increased in size, and gradually presented a verrucous surface. Extension occurred with some rapidity, the oldest portions healing; when he was first seen nearly the whole left side of the scalp and temporal region, including the adjacent skin of the ear, had been covered by the process. Six months before I saw him another pimple appeared in the left malar skin, which now measured two

inches in diameter. The centre appeared flat, depressed, crusted, and bled easily. The peripheral portion was elevated from a half to one centimetre above the skin level, and was covered by very large papillary growths. The surrounding skin of both lesions was infiltrated, reddened, and beset with many minute abscesses. Healing had occurred over a large part of the left scalp, leaving an active verrucous periphery. There is no history of venereal disease.

Verrucous tissue, and pus from the small abscesses, mounted in potassium hydrate solution, uniformly show an organism existing singly, in pairs, or in small groups, the members of which are capsulated, possess a granular protoplasm which often contains many refractive spherules and occasionally vacuoles; they proliferate by budding. An adventitious capsule is found surrounding many cells. This examination repeated many times gives similar findings.

Tubes of ordinary media were inoculated several times from the verrucous tissue and from the abscesses with no growth except that of cocci and bacilli. Eventually, however, a maltose-agar, prepared after the formula of Sabouraud for the ringworm fungi, was inoculated with pus from the abscesses in the reddened areola, the skin being first cleansed with alcohol. After six days small hyphal colonies were noted on all of the tubes. They increased in size slowly, the hyphæ reached the surface of the tubes, and the substratum presented a moulded appearance. Eventually aërial hyphæ (Plate XXXVII., Fig. 1) covered the whole inner surface of the tube. Under the microscope this aërial structure consists of fine branching threads beset with lateral pedunculated conidia which multiply *in situ* by a budding process. That portion of the growth which infiltrates the substratum is composed of similar hyphæ, which, however, are larger and plainly segmented and produce lateral, sessile, or pedunculated conidia and uni-cellular offshoots. The reverse surface of agar slants exhibits a rich, even, golden-brown color, like that of a well-colored meerschaum. Growth occurs slowly but steadily on potato, blood-serum, gelatin, and in various bouillons. In the last-mentioned



FIG. 1.

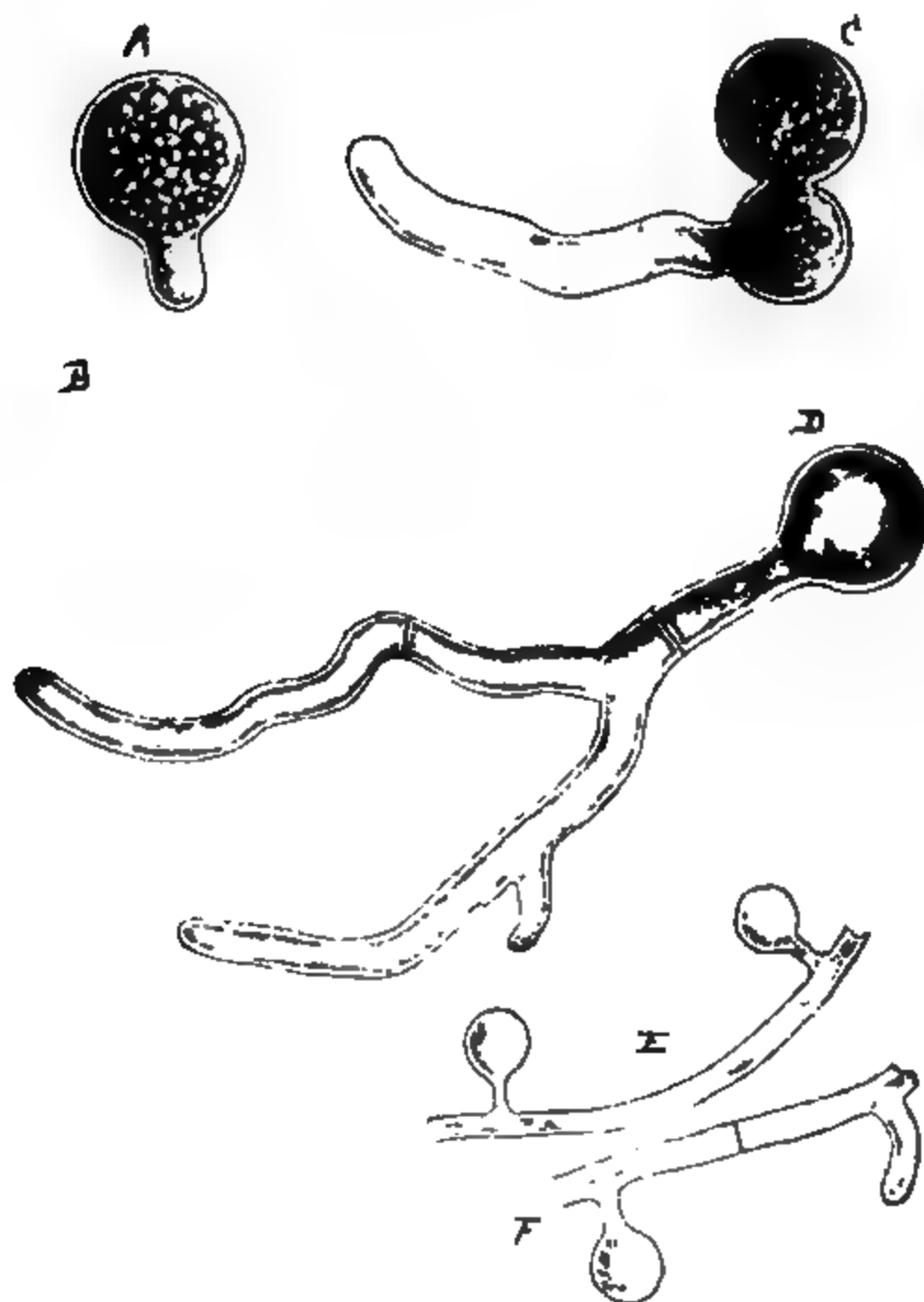


FIG. 2.

medium a coherent, fluffy mass forms, the supernatant fluid remaining clear. The organism does not ferment saccharine solutions.

Proliferation occurs by the segmentation of hyphæ and the abjunction of the resulting oval-cells; by the formation of terminal and lateral spore groups or conidia, and by the budding of ascus-like cells.

A number of subcutaneous and intra-peritoneal inoculations into animals were without result. However, a dog which received an intravenous inoculation died in one month from a mycosis of the entire lung tissue. Cultures of the organism were obtained from the nodules comprising the consolidation. Microscopically, the organisms as they existed in the fresh lung consisted of spherical and budding cells which usually were more or less filled with small structureless refractive spherules. Similar bodies were found free, and it is thought that transition forms have been observed between these and the adult capsulated organism. There were no hyphæ in the lung tissue.

A portion of the nodule containing spherical organisms was inoculated into a hanging drop of bouillon; in a few hours the spherical cells sprouted hyphæ, and within twenty-four hours only a few spherical cells were found, the remainder having developed one or more hyphal elements (Plate XXXVII., Fig. 2). In cultures, also, similar spherical cells filled with the refractive bodies spoken of have been found repeatedly.

Histologically, the human tissue presents two or three interesting features. The verrucous papillæ are remarkably large, and many give off secondary branches. There is an unusual amount of abnormal cornification throughout the epidermis. The number of miliary abscesses is large, and it has been possible to trace the formation of multinuclear giant cells from the cells of the stratum mucosum. A unique feature in the cell-infiltrate of the corium is the strikingly large number of eosinophiles. These are found also in the intra-epithelial abscesses and in inter-epithelial spaces.

Tubercle bacilli could not be found.

Case II. — A Polish woman, of good parentage, and with no

tuberculous or venereal history. The disease began about eighteen months ago as a pustule, and has covered the right side of the face, the bridge of the nose, and has extended moderately on to the supra-orbital skin.

When first seen by Dr. Montgomery, to whom I am indebted for the privilege of studying the case, healing had occurred for the most part, except at the periphery, where there was still a verrucous structure. Located here and there in the periphery and in the central scar tissue were a number of small projecting tubercles, which at first were considered pustules, but on being incised were found to consist of a cellular or mucoid substance. Cultures were at first taken from the verrucous tissue, but the contamination was so great that the tubes were abandoned. At this time an examination of tissue in potassium hydrate solutions showed the presence of numerous "blastomycetes." Subsequently, several of the myxoma-like nodules which were covered with smooth skin were cleansed with green soap and alcohol, the overlying epidermis incised, the soft contents scraped out, and inoculated on various media. It was demonstrated at this time that these nodules contained organisms. Two weeks later the development of a mould fungus was noted in some of the tubes. Growth proceeded slowly, and eventually the organism in its gross and microscopic aspects appears identical with the organism of the preceding case. Animal experiments have not yet been made.

The tissue removed for histological study included a myxoma-like nodule and a small amount of verrucous tissue. The organisms are found in small groups in the corium. There are a number of tubercles resembling closely those of tuberculosis. Tubercle bacilli cannot be demonstrated. As in the preceding case, eosinophiles are very conspicuous as a part of the cell infiltrate.

Case III. — (From Professor Senn's Surgical Clinic. I wish to thank Professor Senn for permission to use this material.) A German woman, 33 years old, giving no personal or family history of tuberculosis, venereal disease, or carcinoma.

Two years ago three pustules appeared simultaneously;

one on the left cheek, the second on the left wrist, and the third on the right buttock. They increased in size, became verrucous, and the last two disappeared spontaneously after about three months. That on the face progressed, and eventually measured about two inches in diameter; presented a depressed centre, and an elevated periphery, composed of very coarse papillary processes; the surrounding areola contained many minute abscesses.

The diseased tissue was removed by Dr. Graham, and through accident was immersed in Zenker's fluid, for thirty or forty seconds. It was immediately put into running water, and washed for two hours. It was feared that cultures might not be obtained because of this treatment. However, a portion of the verrucous tissue was thoroughly disintegrated in a sterile mortar, the resulting pulp suspended in bouillon, and inoculations made on all available culture media and agar plates. After four days rosettes of hyphæ were seen to have grown out from a number of small fragments of tissue which had been transplanted. Growth proceeded as in the two preceding cases, and eventually the same mouldy surface-appearance resulted. Microscopically, this organism differs in no way from the two preceding.

A portion of the tissue was inoculated subcutaneously in the inguinal region of a guinea pig. After a week a nodule developed, which doubled in size at the end of the second week, and was found to contain cheesy pus which on cultures yielded the organism isolated from the human tissue. Spherical capsulated fungus cells were found microscopically; no tubercle bacilli could be demonstrated. A portion of this pus mounted in hanging drop exhibited a growth of hyphæ from the spherical cells, many of which contained the refractive bodies alluded to above.

Aside from the usual features noted in "blastomycetic dermatitis," the presence of large numbers of infiltrating eosinophiles characterizes this case as it does the two preceding. No tubercle bacilli could be demonstrated in the human tissue.

The organisms so far described in connection with this

disease have been of the blastomyces and oïdium types. Hence it is somewhat startling that from each of three successive cases mould fungi were cultivated which appear identical.

The question must soon be decided as to whether these varying organisms obtained from a constant clinical entity are to be considered of common generic or specific dignity. In considering this subject recourse must be had to the observations constantly made by botanists that the members of a particular genus or even of a particular species are subject to variations in morphology and proliferation which may often be remarkable. It is to be noted, also, that many botanists consider blastomyces-like forms and oïdium-like organisms as the conidial stages of somewhat higher fungi. In view of these facts and in view of the fact that the various organisms exist as the cause of a constant clinical entity, the conclusion is reasonable that the fungi are very closely-related organisms. This is substantiated by the observation that the higher types (that is, the mould fungi) possess all the morphological and proliferative possibilities of the oïdium-like and blastomyces-like forms. The conclusion, then, seems reasonable that the latter are adaptation forms or conidial stages of the mould-fungi which have been considered in this communication, aërial fructification having been suppressed in the simpler forms.

It is important to note that Ophüls and Moffit in June, 1900, published an account of a mould-fungus cultivated from the so-called protozoic disease first described by Wernicke and studied in detail later by Rixford and Gilchrist. All previous writers had considered the organism a protozoon. The mould-fungus of Ophüls and Moffit, however, was found in all accessible lesions and a disease was produced in animals similar to that in the patient, and the study of the organism from the lesions in hanging drop cultures proved their identity with the mould-fungus obtained on solid agar. In tissues the organism existed as a spherical capsulated cell, filled with refractive globules like those existing in the organisms isolated from the three cases presented herewith.

A study of the facts at hand points towards the identity of the mould-fungus of Ophüls and Moffit with those cultivated from the three cases of oïdiomycosis of the skin under consideration.

Conclusions.

1. A group of closely-related organisms, which, however, show rather constant differences, exists as the cause of blastomycetic dermatitis (Gilchrist).

2. The simpler organisms probably are adaptation forms or conidial stages of the more complex mould-fungus, possessing, however, fixed specific characteristics.

3. The protozoic (?) disease of Posadas, Wernicke, Rixford and Gilchrist, and others, may be a general disease of which the so-called blastomycetic dermatitis is a local manifestation.

4. Those cases of oïdiomycosis of the skin in which a mould-fungus exists as the cause seem to be characterized by an eosinophilous cell-infiltrate.

(Since the above was written, cultures have been made from two additional cases of "blastomycetic" dermatitis, and a mould-fungus, appearing identical with the three referred to, isolated from each.)

PLATE XXXVII.

FIGURE 1. — Showing aërial hyphæ with lateral conidia, and terminal pseudo-ascospores (?). (Sketched from a culture tube under a low power.)

FIGURE 2. — The development of hyphæ from spherical capsulated spore-containing (?) cells. Fluid from a mycotic pulmonary nodule (dog) containing the organisms was mounted in a bouillon hanging drop and the growth observed.

The nature of the enclosed spherules is uncertain. A, B, C, and D illustrate successive stages of hyphal growth; E and F, the later formation of pedunculated conidia. The larger spherical cells were 10-13 microns in diameter; the conidia 3-4 microns.

CONTRIBUTIONS TO OUR KNOWLEDGE OF COLOR IN
PHOTOMICROGRAPHY.

F. L. RICHARDSON.

The subject of color values has always been perplexing in photomicrography, involving as it does intricate problems in chemistry and physics. For many years the issue was avoided by making special slides stained black or brown, but this involved special staining, and moreover it might not be possible to demonstrate the particular structure by these stains. The introduction of the orthochromatic plate made it possible to take photographs of objects which previously could not be photographed. The orthochromatic plate, however, is not perfectly satisfactory, as it does not give sufficient contrast (all colors having the same value). It is to increase this contrast that color screens or ray filters have been employed.

Before speaking of color screening, it is necessary to understand what is required of the perfect orthochromatic plate, how far the plates approach perfection, and how we can determine the relative merits of the plate. Photographs of the spectrum must of necessity form the most accurate basis for any color comparison or analysis. The apparatus used in this investigation is in its essentials like the apparatus described and used by M. Vogel, and later by L. Vidal in his work on orthochromatism. This apparatus consists of a direct vision spectroscop so mounted in the front board of an ordinary camera (with lenses removed) that the spectrum when projected on the plate will come in the centre horizontally, and at the top of the plate. The back of the camera is constructed in such a manner as to allow of its being moved in the vertical plane, thus making it possible for one to make four exposures on the same plate, and by so doing to make an accurate comparison between them.

The perfect plate for photomicrography would be a plate giving equal photographic intensity to all the colors of the visual spectrum. This degree of perfection has never been obtained. The plates that I have examined can be grouped according to their degree of perfection.

FIG. 1.

APPARATUS FOR MAKING SPECTROGRAPHS.

- A. — Spectroscope.
- B. — Back of camera, carrying-screen, and plate-holder.
- C. — Supports upon which the back (B) may be moved.
- D. — Shutter.
- E. — Color-screen in color-screen holder.

Group I. — Characterized by a very high degree of sensitiveness a little above line D, falling off abruptly on either end, and only slightly sensitive to the greens and blues.

Group II. — Characterized by two distinct maxima — one a little above the D line, and the other in the blue-green. Between these two maxima the sensitiveness falls very considerably.

Group III. — Characterized by having its maximum sensitiveness in the blue (as with ordinary plates), with lesser bands of sensitiveness extending below the D line.

Group IV. — Characterized by bands of sensitiveness extending below line D, with greatest intensity in the yellow-green and falling off at the violet end before H₂.

Group V. — This group most nearly approaches perfection. It is characterized by a sensitive band well below line D and somewhat below the red end of Groups III. and IV. This plate gives an almost uniform degree of sensitiveness with a maximum intensity in the green.

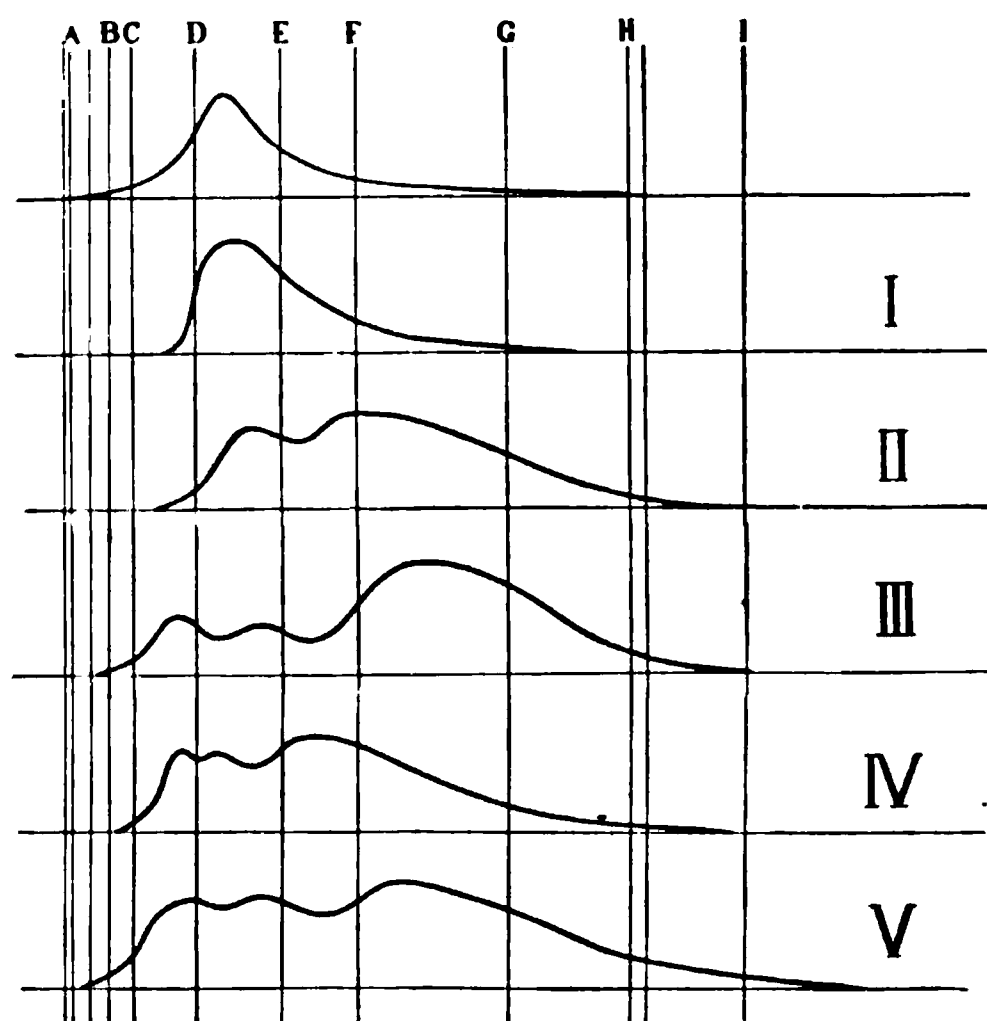


FIG. 2.

The upper curve shows the visual intensity of the spectrum (from Fraunhofer). Curves I., V. represent the photographic intensity of the spectrum taken on plates from group of corresponding number.

Group I. Cramer isochromatic (slow).

Group II. { Standard orthochromatic (slow).
Forbes orthochromatic (slow).
Carbutt orthochromatic.
Otto Perutz.

Group III. { Lovell color-differentiating.
American spectrum plate.

Group IV. Cadett & Neal spectrum plate (slow).

Group V. International "Erethro."

If sensitiveness to the spectrum were the only feature to be considered in the selection of a plate for photomicrographical

Electric arc.....	
Picric acid.....	
Aurantia.....	
Cresoidin	
Congo Red.....	
Eosin.....	
Carbol fuchsin...	
Haematoxylin....	
Methylene Blue..	
Green Glass.....	
Methyl Green....	
Quinine Sulphate	



Methylene Blue

Methyl Green.

Picric acid.

Picric acid.

Methylene Blue.

Carbol fuchsin

FIG. 3.

EXPLANATION OF PLATE.

This plate is a reproduction of spectrographic analysis of some of the common stains. The red end of the spectrum is on the left. The principal Fraunhofer's lines are marked.

The name of the stain is on the left, while on the right is the name of the proper screen to use to increase the photographic intensity. To decrease the contrast use a screen of the same color as the stain.

It will be seen that the spectrum of Picric Acid and Aurantia extends farther to the left (red) than the unscreened electric arc. This is on account of the fact that these two stains allow the red to pass through and that the *exposure is sufficiently increased to allow these rays to affect the plate.*

work a plate from Group V. would hold the first place, but the general working of the plate as well as the keeping qualities are factors that must be considered. For practical work and keeping qualities no plate that I have examined surpasses the Cadett & Neal Special Slow Spectrum Plate. It is this plate which is used in the Sears' Laboratory and on which the spectrographs which follow were taken.

The object of using color screens in any branch of photography is either to increase or decrease the photographic intensity of a color. The law¹ upon which the use of color screens is based is:

1st. — To increase the photographic intensity of a color, a screen of complimentary color should be used.

2d. — To decrease the photographic intensity of a color, a screen of the same color should be used.

This law holds good for all branches of photography whether by transmitted or reflected light, and is not dependent upon the position of the screen; *i.e.*, whether the screen is placed between the source of illumination and the object; between the object and the objective lens; or between the lens and the plate.

To determine the photographic complement of a color is not as simple as it might at first appear; first, because the photographic intensity of the spectrum colors varies greatly from the visual intensity (see Fig. 2); second, because the visual spectrum extends below the lowest photographic rays and the photographic spectrum extends above the highest visual rays. On account of these facts it is more accurate to make spectrographic analysis of the stains and color screens than to make simple visual analysis.

The same plate and source of light must be used as in taking the photomicrograph, because, as has been shown above, plates of different makes may differ greatly in their degree of sensitiveness to different parts of the spectrum, and it is a well-recognized fact that different illuminating agents give different spectra. The object for which one should

¹ Stated by J. G. Hubbard in the Journal of the Boston Society of Medical Sciences, Vol. III., No. 11.

strive in the analysis of stains and screens is to imitate as exactly as possible the conditions that will exist in the process of photomicrography.

In the following table of spectrographs the electric arc is used as a source of light and the photographs were taken on Cadett spectrum plates. Color screens were used in preference to cells of fluid, as these screens are much more convenient than cells and are quite as satisfactory. These color screens are made by soaking a cleared lantern slide in a solution of the desired stain until the gelatine is saturated, then rinsing and removing the surface liquid with a cotton pad. The screen is then dried and covered with a cover-glass as in mounting a lantern slide. The depth of color in these screens is dependent upon the degree of concentration of the staining solution rather than upon the length of time the plate is soaked.

In concluding I wish to acknowledge the kindness of Professors Councilman and Trowbridge and Drs. Wright and Derr in giving me the benefit of their extended experience and knowledge of this subject.

A CASE OF NOMA OF THE AURICLES DUE TO THE STREPTOCOCCUS PYOGENES, AND ITS BEARING ON THE ETIOLOGY OF NOMA IN GENERAL.

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Noma is undoubtedly a rare disease. According to Ranke,¹ in about 10,000 cases he met with it only twice. Of those parts of the body upon which it has occurred, the ears have least often been attacked. The etiology of noma is still in the dark, not from the lack of attempts to discover it, but rather because investigators have arrived at such diverse conclusions in regard to it. I report the following case not only because it is an example of an extremely rare affection of the ears, but also because it seems to throw considerable light upon the etiology of noma in general. The case was admitted to the Massachusetts Charitable Eye and Ear Infirmary during the service of Dr. J. Orne Green, to whom I am indebted for the privilege of reporting a summary of its clinical features.

Sarah W., aged 5 months, admitted Jan. 16, 1901. Family history unimportant. Previous history, always well and strong until present illness. For five weeks previous to admission there was a discharge from each ear. One week previous to admission the parents noticed that on the right side the discharge was irritating the skin of the external auditory canal and lobule of ear. On admission there was a purulent discharge from both ears, the tympanic membranes were apparently partially destroyed, and just in front of and below the lobule of the right ear there was a deep round ulcer, 7 mm. in diameter, with irregular base and slightly overhanging edges. The base of the ulcer was covered with pus. The surrounding parts were red and thickened. The left ear showed no ulceration, but on the helix there were two or three reddened spots. Despite treatment by the actual cautery and local applications of antiseptics, the ulcerative process on the right side gradually spread, involving the cheek;

and on the 5th day after admission there was also a definite ulcer just below the left auricle. On the 7th day there was noted on the right side near the ulcer a reddened area about 1.4 cm. in diameter, but the ulcer seemed to spread by direct extension into sound tissue. On the 7th day also it was noticed that the left great toe, and to a less extent the little finger of the right hand, were red and swollen. On succeeding days other joints of the fingers and toes became affected in the same way. The appearance of some of the joints would vary greatly even during the course of one day, now appearing more and now less inflamed. The same thing was observed in the case of the reddened area near the ulcer of the right ear, which for two days became almost invisible, and then again reappeared as a much larger area with an ill defined border. There was considerable diarrhoea, and the child took its nourishment poorly. Both the local and the general condition of the patient steadily became worse, and the child finally passed into a semi-comatose condition and died on the 17th day after admission.

AUTOPSY by Dr. Verhoeff, 12 hours after death. Body 56 cm. long, fairly well nourished, slight rigor mortis. Lividity of dependent parts. No post-mortem decomposition. The metatarso-phalangeal joint of great toe of left foot is swollen, and contains yellowish pus; the first joint of the same toe is also swollen, but contains a clear fluid. The metatarso-phalangeal joint of fourth toe of right foot is swollen and contains pus. All of the metatarso-phalangeal joints of the right hand, except that of the thumb, are swollen and contain pus. Palm of left hand is swollen and contains a clear fluid. Large joints of body apparently unaffected. Abdomen greatly distended. Peritoneal cavity free from fluid. Pleural cavities free from adhesions and fluid. Pericardial cavity does not contain an excess of fluid. Lungs: Pleural surfaces are congested and show many emphysematous elevations. On section there are red and grayish areas scattered throughout both lungs, but they are most numerous in left lung. These areas are firm, friable, and removed portions sink when placed in water. There is little or no edema.

A purulent fluid can readily be expressed from the smaller bronchi. Heart: Foramen ovale patent, but well protected by valve. Left ventricle distended with blood. Heart otherwise apparently normal. Ductus arteriosus not patent. Spleen not greatly enlarged, rather firm; on section lymph nodules and trabeculæ distinctly seen; pulp not increased, dark in color with many large red areas scattered over cut surface. Gastro-intestinal tract: Stomach apparently normal. Intestines greatly distended with gas. Small intestines normal. The lower two-thirds of the colon is congested and shows several fairly large patches, which are raised above the surface and irregular in shape. The liver, kidneys, pancreas, bladder, uterus, tubes, and ovaries are normal.

Head. — On the right side there is an oval almost black area measuring $2\frac{1}{4} \times 1\frac{1}{2}$ cm. which involves the tragus and lobule of the ear and a portion of the cheek adjacent to the latter, and extends into the external auditory meatus. The area is sunken considerably below the level of the surrounding parts and gives off a foul odor. Its margin is sharply defined and there is no induration. The greatest loss of substance is within the concha near the external auditory meatus, where there is also a slight amount of pus. Except for this, the entire area is practically dry or at most only slightly moist. There is considerable hyperæmia and desquamation of the surrounding skin. On the left side of the head the same condition is evidently present, but it is not so far advanced. There is an area 1 cm. in diameter, involving the lobule and the tissue beneath it, which is similar in character to the larger one on the right side. In the neighborhood of this area, but not connected with it, there are two red maculæ 4 mm. in diameter. Within the concha there is a loss of substance extending into external auditory meatus. Here there is a slight amount of pus. The surrounding skin is more hyperæmic than on the right side.

The surface of the brain is not congested, the venous sinuses are free, and there is no evidence of extension of inflammation from middle ear or mastoid into the cranial cavity. On section the brain is apparently normal.

BACTERIOLOGICAL EXAMINATION. *Ulcers of Ears.*—Smears show great numbers of small cocci which are usually in chains, a less number of small bacilli with rounded ends and a few large cocci. The cocci and a few bacilli stain by Gram. Before the death of the patient, blood serum cultures were taken on several occasions by Dr. Lecompte. All of them showed a small bacillus with rounded ends, actively motile, liquefying, producing a foul odor, not staining by Gram, and otherwise presenting the cultural characteristics of the *proteus vulgaris*. In addition to this bacillus the *streptococcus pyogenes* was obtained in one culture. Cultures taken at the autopsy show only the bacillus just described. An anærobic culture, taken according to the method recently recommended by Wright¹, shows apparently this same bacillus. *Mastoid Cells*: Smears from mastoid cells of left ear show the predominating organism to be a coccus in chains. A number of bacilli similar to some of those found in smears from the ulcers of the auricles are also present. There are also a few large spore-bearing bacilli. *Joints*: Smears made from pus obtained from the small joints of hands and feet show cocci, often in chains, and varying greatly in size. Cultures made from two of the joints show a pure growth of the *streptococcus pyogenes*. Anærobic cultures are negative. *Lungs*: Smears show the presence of numerous cocci in chains and a few bacilli. The cocci are mostly within cells. Cultures show the *proteus vulgaris* and streptococci. *Liver*: Cultures show a pure growth of the *streptococcus pyogenes*. *Blood*: A culture from the blood of the left ventricle of the heart shows the *streptococcus pyogenes* and a few bacilli. These bacilli do not liquefy blood serum and produce no odor. They have ceased to grow after the second transplantation on blood serum.

MICROSCOPIC EXAMINATION.—Tissues were fixed in Zenker's fluid, imbedded in celloidin, and sections of them stained in hematoxylin and eosin, except as otherwise noted. *Ulcers of the Ears*: Several pieces of tissue were removed from the ulcers, so as to include both normal and necrotic

¹ Jour. Bost. Soc. Med. Sciences, Dec. 1900, p. 114.

tissue. The histological changes are the same on both sides. As the skin surface is traced from the comparatively unaffected parts, it is seen rather suddenly to become granular, to stain more intensely with eosin, and to lose the outlines of its individual cells. At the point where the epithelium becomes necrotic the corium and subcutaneous tissue have also undergone hyaline degeneration, so that a line of division between corium and epithelium can no longer be made out. The floor of the most necrotic portion of the ulcer is densely packed with leucocytes in varying stages of necrosis, while beneath it there are few, and in some places apparently no pus cells, the tissue simply presenting the appearance of hyaline necrosis. Deeper down the tissue loses its hyaline appearance, and stains in a normal manner. The deeper tissues, however, including the adipose tissue, are congested, and greatly infiltrated with leucocytes. Three zones, therefore, can be distinguished — an outer zone of dense purulent infiltration, a wider middle zone of hyaline necrosis, and an inner zone of comparatively normal tissue. The leucocytes are most necrotic at the inner and at the outer margin of the zone of hyaline necrosis, thus giving the impression that they are attempting to enter the latter both from within and without, but are destroyed before they can do so. This would indicate that the pus in the outer zone did not come from the tissues lying immediately under it, but probably from some other part of the ulcer, or possibly from the purulent discharge of the otitis media. This is further suggested by the fact that the stratum corneum of the epidermis, at a short distance from the margin of the ulcer, is infiltrated with pus cells, while scarcely one of the latter can be seen in the other epithelial layers. There are no areas of necrosis in the deeper tissue, and thrombosis is not to be observed in either the smaller or larger vessels. There is a marked absence of any chronic inflammatory processes in the tissues surrounding the ulcer. Sections stained by the Gram-Weigert method show masses of cocci so dense as readily to be recognized by the low power of the microscope. As seen by the low power they are apparently confined to the

necrotic tissue. Under oil immersion they appear as very small cocci, usually in short chains, less often in pairs, and are seen to be present not only in the necrotic tissue, but also for a considerable distance in the underlying tissue. In many places they seem to be tightly packed in distended lymph spaces. This is especially noticeable in the zone of simple hyaline necrosis, where there has been no leucocytic invasion, and in this zone the cocci seem to be most numerous. On the surface comparatively few bacteria are to be seen, and these are almost always cocci, although a bacillus may occasionally be seen. Paraffin sections stained in Ziehl's carbon-fuchsin twenty-four hours, and decolorized in seventy per cent. alcohol, as well as sections stained in Stirling's gentian violet, also show only cocci in the tissues.

Temporal Bones: Both temporal bones were fixed in ten per cent. formalin, followed by alcohol, and decalcified in five per cent. nitric acid. On section macroscopically they present the same appearance, namely, that of suppurative otitis media and mastoiditis. The tympanic membrane on each side is totally destroyed. Celloidin sections of the left temporal bone show the mastoid antrum and mastoid cells packed with polynuclear leucocytes, and their walls lined with considerable newly formed granulation tissue. The bone structure has not been injured, but the epithelium, and in many places the periosteum, lining the air spaces, has been destroyed. Practically the same condition is present on the right side. On neither side is the labyrinth involved, although the suppurative process has extended to within a short distance of it. Sections stained by the Gram-Weigert method show streptococci, often in long chains, in almost all of the mastoid cells. They are most numerous in the pus of the antrum. No other organisms can be found even in sections stained twenty-four hours in carbol-fuchsin. The streptococci are so numerous, however, that other organisms, if few in number, could easily be overlooked.

Lungs: Sections made from some of the areas of consolidation show most of the alveoli filled with polynuclear leucocytes and a few epithelial cells, with very little fibrin or red

corpuscles. In a few of the alveoli fibrin is the principal element, while in others, also few in numbers, red blood corpuscles predominate. The smaller bronchi are filled with polynuclear leucocytes, desquamated epithelium, epithelioid cells, and red blood corpuscles. Almost every bronchus to be seen is surrounded by a zone of congestion and hemorrhage. The larger bronchi are also affected, the lining epithelium is in many places destroyed, and the walls are coated with red blood corpuscles, polynuclear leucocytes, and necrotic epithelial cells. The bronchial lymph nodes are greatly congested and infiltrated with polynuclear leucocytes. Sections stained by the Gram-Weigert method show very small cocci, usually in pairs, but sometimes in long chains, within both the alveoli and the bronchi. The cocci, however, are not so numerous as the smears would seem to indicate.

Colon. — The mucosa is congested, and in many places necrotic and coated with fibrinous membrane. In other places it is replaced by fibrin. The submucosa is infiltrated with fibrin and pus cells. The muscular tissue is little involved. The mesenteric lymph nodes are congested and infiltrated with polynuclear leucocytes. The Gram-Weigert stain shows very few bacteria, only a few cocci in pairs and short chains and an equal number of bacilli being seen in the tissues. The *heart* shows nothing worthy of mention. The *liver*, *spleen*, and *kidneys* show acute congestion. The *pancreas* is apparently normal. In sections stained by the Gram-Weigert method, streptococci can be seen in the blood-vessels of all the tissues examined. They can be seen occluding some of the capillaries of the liver, and a few masses of them can be seen in the spleen pulp.

Diagnosis. — Streptococcus otitis media and mastoiditis, streptococcus gangrenous ulceration of auricles and cheeks, streptococcus synovitis, streptococcus broncho-pneumonia, streptococcus septicæmia, croupous colitis.

It seems to me that there can be little question that the gangrenous ulceration of the auricles and cheeks was the result of infection by the purulent discharge from the middle ears. When it is considered that the streptococcus is com-

monly found in otitis media, it seems remarkable that such an infection does not occur more often. In noma of the mouth there is usually a history of some previous disease, often one of the exanthemata, but in this case no such history could be obtained, thus rendering the infection less easy to explain on the grounds of lowered resistance. It is possible that the virulence of the organism is a more important factor than the lack of resistance of the patient. The streptococcus septicæmia, synovitis, and pneumonia, while not of course alone sufficient to prove the nature of the infection in the local ulcers, nevertheless are highly confirmatory in this regard, and, in addition, indicate either that the patient possessed very little resistance towards the streptococcus, or that the latter was extremely virulent.

In the literature I have been able to find thirteen cases * of noma auris, most of them very incompletely reported. The ages varied from three weeks to four years. Eight cases were associated with otitis media, while in the remaining cases no mention was made of otitis media, although in some of them it no doubt was present. In three cases the affection was bilateral. Death resulted in all but one case, that of Hutchinson², who cauterized the ulcer with acid nitrate of mercury. None of the cases were investigated histologically, and but one of them bacteriologically. The latter was reported by G. M. Smith³, who obtained from the ulcer of the auricle and from the longitudinal sinus cultures of a short non-motile bacillus with rounded ends, often arranged in pairs or chains. The bacillus stained readily, but the centre often remained unstained, and the organism did not liquefy gelatin. It was regarded by Smith as identical with the bacillus of Schimmelbusch¹¹. The absence of an histological examination of the tissues for bacteria, however, renders this case of little value from the standpoint of etiology. The description of the bacillus found by Smith does not seem to exclude members of the colon group.

Etiology of Noma in General. — Klautsch⁴, after reviewing the literature, concluded that noma was not due to any

* Eitelberg cites four cases, published in periodicals that I am unable to obtain.

specific bacteria, but that the various putrefactive bacteria, which remain inactive on a healthy mucous membrane, set up the process of necrosis in a mucous membrane whose nutrition has been disturbed. More recently Krahn⁵ has investigated two cases of noma, and has given a careful review of the literature. He considers noma to be the result of a mixed infection by the mouth bacteria, especially the spirillum sputigenum and spirochaete dentium, which he claims to have found deep down in the apparently normal tissue about the gangrenous areas. Other observers have attributed the disease to various sorts of bacilli, Petruschky⁶ claiming the diphtheria bacillus as the etiological factor. Perthes⁷ considered the disease to be due to the streptothrix. Samson⁸ in 1878, and Morse⁹ in 1885, described actively moving crystalline bodies in the blood of a case of noma.

Ranke¹ seems to be the only investigator who has taken the view that noma is due to the streptococcus. He studied three cases following measles — two of the face and one of the vulva. All three cases showed practically the same microscopic appearances. He found in the tissues almost exclusively cocci in long and short chains, giving the impression of a pure culture. He cited Koch¹⁰ as authority for the statement that streptococci will produce a progressive necrosis in field mice.

Dr. Councilman and Dr. Mallory have kindly given me permission to report here the cases of noma that have come to autopsy at the Boston City Hospital. I was able to find five such cases, as follows:

Case 1. Path. Rec. 97/64. Age 4. *Clinical diagnosis:* Measles and broncho-pneumonia. *Anatomical diagnosis:* Acute rapidly spreading necrosis of soft tissues of upper and lower jaw and cheek, with necrosis of the margins of the inferior and superior maxillary bones, necrosis of turbinate bones and vomer. Necrosis of the soft tissues of the nose, palate, pharynx, uvula, and tonsils. Purulent fluid in the antrum of Highmore, acute suppurative inflammation of left middle ear and mastoid process. Acute purulent bronchitis and purulent broncho-pneumonia of both lungs. Acute

general lymphatic hyperplasia. Acute splenitis. Acute parenchymatous degeneration of liver and kidneys. Loosening of teeth in upper jaws. *Bacteriology*: Smears from pus of lung show pus cells, streptococci, and a few short bacilli. Cultures, — Necrotic areas of soft tissues of upper jaw and lower lip show a variety of organisms among which are streptococci, staphylococcus pyogenes albus, colon bacillus, and a few diphtheria bacilli. Trachea shows a variety of organisms, few streptococci, and staphylococcus pyogenes albus. Right lung, lower lobe, shows few streptococci and a very few diphtheria bacilli, middle lobe, many streptococci, a few diphtheria bacilli, and the colon bacillus. Spleen shows a very few diphtheria bacilli. Kidney shows colon bacillus. Right middle ear, few diphtheria bacilli and staphylococcus pyogenes albus. Left middle ear, negative.

Case 2. Path. Rec. 97/89. Age 7. *Clinical diagnosis*: Diphtheria and scarlet fever. *Anatomical diagnosis*: Gangrene of mucous membrane of mouth. Subcutaneous miliary hemorrhages over abdomen and lower chest. Acute broncho-pneumonia of both lungs, acute general lymphatic hyperplasia. *Bacteriology*: Cultures, — Trachea, negative. Right lung, lower lobe, many streptococci, and a few diphtheria bacilli. Liver, many streptococci, seven colonies of diphtheria bacilli. Spleen, pure streptococcus. Kidney, few streptococci.

Case 3. Path. Rec. 97/136. Age 4. *Clinical diagnosis*: Diphtheria. In this case the ulcerative necrosis apparently began in the tonsils and extended over the root of the tongue and over the anterior surface and tip of epiglottis, where it was superficial. *Anatomical diagnosis*: Diphtheritic rhinitis. Gangrenous stomatitis. Tonsillitis and peritonsillitis. Diphtheritic and gangrenous gastritis. Diphtheritic duodenitis. Acute broncho-pneumonia. Chronic interlobular pleurisy. Acute splenic tumor. Lymphatic hyperplasia, cervical and perigastric regions. Acute suppurative otitis media with extension to mastoids. *Bacteriology*: Cultures, — Right tonsils, variety of organisms, diphtheria bacillus present. Lung, abundant streptococcus. Liver and spleen, diphtheria bacilli

and streptococci. Kidney sterile. Stomach, variety of organisms, diphtheria bacillus and streptococcus abundant. Right ear, diphtheria bacillus and streptococci.

Case 4. Path. Rec. 96/133. Child 84 cm. long. *Clinical diagnosis:* Noma of cheek and mouth. *Anatomical diagnosis:* Gangrene of mouth; with extension through cheek — gangrenous ulceration of cheek; necrosis of upper jaw; acute broncho-pneumonia; hyperplasia of splenic follicles, and slight parenchymatous degeneration; granular degeneration of liver; anæmia and fatty degeneration of kidneys. *Bacteriology:* Cultures,—heart, colon; liver, sterile; spleen, sterile; kidney, staphylococcus albus and aureus, colon bacillus, and a large liquefying bacillus. *Histological examination:* Sections of the gangrenous area of the cheek show a superficial area which does not stain, is apparently gangrenous. There is no reaction on the part of the tissues beneath. In places there is a very slight purulent infiltration, but in general there is not cellular hyperplasia, and the gangrenous area on the surface passes more or less diffusely into the tissue beneath. In the muscle of the cheek there is in places a slight increase in the inter-muscular tissue. The absence of reaction is the most striking and interesting thing in the sections. A section through the subcutaneous fat, where the gangrenous area is intact with this, shows the same thing — an entire absence of inflammatory reaction. On the section of the cheek no bacteria were found in the tissues either by Löffler's or Weigert's stain. In the Weigert stained specimen there is a large mass of organisms clinging to the gangrenous area. No particular organism predominates, chief organisms consisting in cocci, with a few bacilli.

Case 5. Path Rec. 99/64; age, 23 months. Noma of mouth following diphtheria. *Anatomical diagnosis:* Acute broncho-pneumonia, bronchiectasis; acute muco-purulent bronchitis; general hyperplasia of lymph nodes; cancrum oris; inferior maxilla denuded of soft parts; ulceration of tonsils and epiglottis; acute suppurative otitis media; hydrops antri; fatty degeneration of kidneys. *Bacteriology:* Cultures,—Heart and spleen, streptococcus pyogenes in pure

culture; liver, lung tissue, abscess of lung and both middle ears, all show streptococcus pyogenes and other organisms. Larynx and both ears show in addition diphtheria bacilli.

In only one of these cases (Case 4) was there an histological examination of the tissues involved in the ulcerative stomatitis. Through the kindness of Dr. Christian, however, I was able to obtain the tissues saved from Case 5. I find that sections of this tissue, stained in hematoxylin and eosin, show very much the same appearance as that described in Case 4. There is presented a picture of complete necrosis, in which not a single pus cell can be seen. The necrotic tissue is granular, and stains by eosin, the necrotic muscle fibres taking the deepest stain. In it there are numerous masses of brown pigment, evidently derived from blood extravasations. The surrounding tissues are congested and considerably infiltrated with polynuclear leucocytes. There are also present a few lymphocytes and plasma cells; but here, too, the absence of chronic inflammatory reaction is marked. No absolutely sound tissue is present in the specimen. Sections stained by the Gram-Weigert method show, under the low power of the microscope, masses of bacteria collected most noticeably around and about the brown pigment just mentioned. In the comparatively normal tissues these masses of bacteria cannot be seen. Under oil immersion innumerable bacteria in great variety are seen. The most prominent organisms are streptococci in short and long chains and long thread-like bacilli. The latter do not stain deeply, but can readily be made out. There are some areas in which no organisms can be seen; others in which only the long thread-like bacilli can be recognised, and still others in which only cocci, apparently streptococci, are present. In the most nearly normal tissue cocci alone are found, and these are usually in chains. In the sections, taken as a whole, the streptococcus is undoubtedly the predominating organism.

It will be seen that so far as general infection was concerned, the streptococcus played a prominent part in all but one of these cases. In Case 1, the only case in which it was definitely stated that cultures had been taken of the local

PLATE XXXIX.

Noma of the right auricle in a child of 5 months. The gangrenous ulceration involves the tragus and lobule of the ear, a portion of the cheek, and extends into the external auditory meatus. A similar but less extensive process is present on the other side. Photograph taken 6 hours after death

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ulcer, streptococci were obtained in the latter. In Case 4, the case in which streptococci were not obtained in any of the cultures, no cultures were taken of the local ulcer. In the two cases, 4 and 5, that were examined histologically, one of them showed streptococci present in great numbers, while in the other no organisms of any kind were found in the tissues involved in the stomatitis. Taken alone, these cases do not seem to show a great deal, but considered in connection with my own case, in which the streptococcus was the only organism found in the tissues, they are certainly suggestive.

It is interesting to note that in twenty cases of noma cited by Krahn,⁵ in no more than three cases were cocci absent. In three cases, however, they were present only in cultures. So far as I can find, in no case has a condition similar to noma been definitely produced by inoculation of bacilli. On the other hand, the work of Koch¹⁰ leaves little doubt that the streptococcus is capable of producing in field mice a condition practically identical with noma. And my own case, as well as the cases reported by Ranke, seem to indicate clearly that the streptococcus is capable of producing noma. It should be remembered, too, that the streptococcus is an organism whose pathogenicity to man has been amply demonstrated, and that it is capable of producing a variety of pathological conditions. It would seem, therefore, that while the evidence is not perhaps sufficiently strong to prove that noma is invariably due to the streptococcus pyogenes, nevertheless it seems to point more strongly towards this organism as the chief etiological factor than to any other organism yet described.

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CLASSIFICATION OF CANCER UPON AN EMBRYOLOGICAL BASIS.

W. F. WHITNEY.

In the Middleton-Goldsmith lecture, Professor C. S. Minot called attention to the close analogy between numerous pathological processes and those which occurred under normal conditions. He further insisted on the necessity of more clearly differentiating the tissues according to the embryological layer from which they originated, in their pathological study. It is especially among the new growths that this differentiation is most readily applicable.

I shall attempt, briefly, to sketch a classification by which cancers can be referred to a germ layer from which the particular epithelium that forms their characteristic constituents originates. This can be made with but little alteration of the existing nomenclature, and with the addition of only a few new terms.

In the first place, all cancers should be referred to as of epiblastic, mesoblastic, or hypoblastic origin. Then in a broad sense the epithelium of each of these layers can be divided into the simple covering epithelium and that which is more highly specialized, chiefly in glandular formation. I would, therefore, subdivide each of the three groups according as it arises from the simple covering, or specialized epithelium.

Tumors arising from a simple covering layer should be designated by the termination *oma* added to that of the kind of epithelium. The terms epithelium and mesothelium, as designating the upper and middle layers, are already in general use and accepted. To these *hypothelium* should be added, which designates the epithelium of the under layer, or hypoblast.

The term hypothelium has been used rather than entothelium in order to avoid confusion which would naturally arise between it and endothelium.

For those arising from the differentiated epithelium, I would preserve the term cancer preceded by the adjective designating the kind of epithelium of which it is composed, viz., epithelial, mesothelial, and hypothelial cancers. The following table will epitomize what I have just said: —

Cancers.

I. Of Epiblastic Origin.

- a.* epithelioma (lip).
- b.* epithelial cancer (breast).

II. Of Mesoblastic Origin.

- a.* mesothelioma (peritoneum).
- b.* mesothelial cancer (ovary).

III. Of Hypoblastic Origin.

- a.* hypothelioma (œsophagus).
- b.* hypothelial cancer (intestine).

The names in parenthesis indicate a type of each one of these.

With Professor Minot's kind permission I would add his table giving the epithelia and the different germ layers from which they arise.

CLASSIFICATION OF THE TISSUES.

A. ECTODERMAL.	B. MESODERMAL.	C. ENTODERMAL.
1. <i>Epidermis.</i>	1. <i>Mesothelium.</i>	1. <i>Notochord.</i>
<i>a.</i> Epidermal appendages.	<i>a.</i> Epithelium of	2. <i>Epithelium of</i>
<i>b.</i> Lens of eye.	peritoneum,	<i>a.</i> Digestive tract,
2. <i>Epithelium of</i>	pericardium,	œsophagus,
<i>a.</i> cornea.	pleura,	stomach,
<i>b.</i> olfactory chamber.	urogenital organs.	liver,
<i>c.</i> auditory organ.	<i>b.</i> Striated muscles.	pancreas,
<i>d.</i> mouth	2. <i>Mesenchyma.</i>	small intestine,
(oral glands),	<i>a.</i> Connective tissue,	yolk-sack,
(enamel organ),	smooth muscle,	large intestine,
(hypophysis).	pseudo-endothelium,	cæcum,
<i>e.</i> anus.	fat-cells,	vermix,
<i>f.</i> chorion,	pigment cells.	rectum,
Fœtal placenta.	<i>b.</i> Blood.	allantois (bladder).
<i>g.</i> amnion.	<i>c.</i> Blood vessels.	<i>b.</i> Pharynx,
3. <i>Nervous system.</i>	<i>d.</i> Lymphatics.	Eustachian tube,
<i>a.</i> Brain,	<i>e.</i> Spleen.	tonsils,
optic nerve,	<i>f.</i> Supporting tissues,	thymus,
retina.	cartilage,	parathyroids,

CLASSIFICATION OF THE TISSUES. — *Continued.*

A. ECTODERMAL.

B. MESODERMAL.

C. ENTODERMAL.

b. Spinal cord.

bone.

thyroid.

c. Ganglia.*g.* Marrow.*c.* Respiratory tract,*d.* Neuraxons.

larynx,

trachea,

lungs.

It will be noticed, in the above classification, that endothelioma has not been mentioned, but at present as the endothelium is considered to arise from the mesenchyma, and not from the mesothelium, it is best preserved under its present name and should occupy an intermediate position between cancer and sarcoma.

THE VALUE TO PHYSIOLOGY OF ANTHROPOMETRIC TESTS
AND MEASUREMENTS IN THE FORM OF STATISTICS AND
THEIR IMPORTANCE TO EDUCATION.¹

H. G. BEYER.

The great value of statistical records to the physiologist, as a means of studying certain physiological events, is, I believe, generally recognized. From the point of view which interests us most, these refer principally to changes in growth and development as they follow a certain definite chronological order. Thus, for example, if we were in the possession of a complete set of statistical records, taken in the order in which they occur or succeed each other, of the developmental stages of a number of human beings and their component organs, from the moment of their conception to the time of their death, who can doubt that such records would serve to contribute very largely also to the physiological history of the growth and development of an average human life ?

Up to the present time, however, we have but a few scraps of such a history. Imperfectly known as are these physiological events, we have long since attempted to promote and further them by a process known as training or education, here used in the broadest sense. In the course of time we have found out that the exercise of the normal function of any organ or tissue, besides giving us a measurable amount of work, will exert a reflex influence upon the structure, growth, and working capacity of that organ or tissue. The results of experiments in this direction have invariably shown that these assumptions were justified under certain well-defined conditions and circumstances. In the living animal body, under normal conditions and at rest, we find a condition of tissue-equilibrium.

¹ Read in Section on Anthropometry at the meeting of the American Association for the Advancement of Physical Education, Fayerweather Hall, Columbia University New York, April 19, 1901.

Tissue-equilibrium exists when assimilation and disassimilation are of equal value; it is disturbed by outside stimuli or irritants, because most of these do not affect assimilation and disassimilation alike.

It is one of the most important provisions in living things that, after an irritant ceases to act, the tissues return to the state of equilibrium, owing to the internal auto-reconstructive tendencies of a living organism.

If, for instance, a certain irritant or stimulus, as exercise, had acted upon dissimulation, upon the destructive phase of tissue-metamorphosis, in a living substance, the assimilative phase would under normal conditions become secondarily engaged in making good the loss occasioned by the stimulus acting upon the dissimilative phase in the process. When, however, an irritant or stimulus, with an effect upon dissimulation alone or almost alone, has continued to act for a certain length of time, there is finally brought about a condition in the living substance, due to an accumulation of waste-products, and this condition is known in physiology as *fatigue*. — The essential characters by which this condition is recognized, are: lowered excitability and a decrease in the amount of work done in a given time by the particular organ or tissue concerned. A careful study of this condition in its relation to training and education is of the utmost importance.

Let us, therefore, try to give it a place in our scheme and so help to fix its relation to our work in our minds. We know that absolute inactivity of any organ or tissue is followed by a process known as degeneration, and that activity, carried beyond the normal range of the endurance of an organ, is followed by exhaustion and paralysis. Between these two extreme limits lies the normal range, and somewhere within it we must find the optimum point of activity corresponding, at the same time, to the maximum capacity for work and which has the most favorable reflex influence upon the normal growth of any organ concerned.

Both degeneration and exhaustion border on the domain of pathology and are, therefore, rarely subjected to investigation on the part of the physiologist. But shortly before

we reach the point of exhaustion, on the downward arm of our binomial curve, we arrive at a point where we meet with a condition known as fatigue, and this being still considered within the physiological range, has been formally studied and investigated by some of our best physiologists. — As teachers, as educators, as the professed promoters of normal growth and development in human beings, entrusted to our care by a confiding public, our first duty must be to do no harm under any circumstances. Our next duty is to influence for good the education of our charges. In order to discharge our full duty in this regard we must know (1) the danger points and signals, and (2) also the point or the conditions under which our work has its maximum beneficial effect. An acquaintance with that point within the physiological range at which the activity of any organ or tissue which we wish to place under the more favorable condition for development produces its optimum beneficial effect, is a necessary preliminary to success on the part of all educators. This point must lie about midway between the two danger signals, namely: absolute inactivity followed by degeneration, and exhaustion followed by paralysis from over-exertion. It must, moreover, lie at a point before fatigue occurs, for we have already seen that fatigue precedes the condition known as exhaustion and is itself due to the accumulation of the products of wear and tear, hence no longer presenting the most favorable conditions for growth and development.

I know of no instrument that has served to give us more real information as regards the normal or physiological range of functional activity than has the ergograph, simple as it is. The ergograph, at present, appears in two forms. In the case of the original instrument of Mosso, a muscle contracts against the resistance of a constant weight, while with the spring ergograph, employed by Binet, Catell, Franz Hough, and Schenck, the resistance is variable, and allows the contracting muscle of a certain degree of choice or selection. The muscle, here, lifts what it can and no more.

Physiologically considered, the curves produced by Mosso's original instrument and by the spring ergograph respectively

have a significance of far greater difference than would at first sight appear. From a merely mechanical point of view, and somewhat roughly speaking, the difference between the two instruments is practically the same as that between the Sargent chest-weight on the one hand and the Whitely exerciser on the other. If we examine the curves produced by either the ergograph of Mosso and the spring ergograph respectively, and apply to them a certain arbitrary test represented by the formula $\frac{P}{R \cdot r}$, where P. is the power of the neuro-muscular mechanism, R. stands for the resistance offered by the weight, and r. for the rate with which the weight is lifted, we find the difference to be as follows: The above fraction in Mosso's curves is, at first, for a short period equal to one and then rapidly loses, becoming less than one, and, finally, ends at zero for a numerator. In the curves obtained by the spring ergograph, our fraction begins by being at first slightly greater than one, and then slowly reaches a point at which it remains equal to one throughout.

Recent experiments by Verworn on fatigue, both with the ergograph on man and on the frog, with the usual recording instruments, have shown that both in muscle as well as in the central nervous system, excessive activity is followed by fatigue and exhaustion. Fatigue is that condition which is due to the accumulation of the products of wear and tear, and of which CO₂ is undoubtedly one; and exhaustion, on the other hand, is due to the lack of material necessary for the building up of the lost substances, and of which oxygen is at least one. Exercise of an organ stimulates the destructive phase, rest the assimilative phase.

Whenever the dissimilative phase is greater than the assimilative phase, which is the case in excessive exercise, the products of wear and tear accumulate in the tissue, and a decrease in the work done is bound to follow, for this constitutes the condition known as fatigue. Whenever the dissimilative stimulus is exactly counterbalanced by the assimilative phase, it is a sure sign that the neuro-muscular mechanism has reached its maximum point of efficiency and is doing as much as it is capable of doing, but is *not yet fatigued*.

In the curve obtained by the spring ergograph, it would appear that these two phases exactly balance one another, and thus a condition of tissue equilibrium is steadily maintained. The curve, therefore, is not strictly speaking a fatigue curve, but rather a maximum-efficiency curve. In the Mosso curve we meet with a steady increase in the dissimilative phase until the amount of fatigue thus produced prevents the lifting of a given weight, although the neuro-muscular mechanism is still able to lift a smaller one. Applied to our fraction, we find that P. becomes smaller with every new contraction as long as R. r. remain the same, as they must under the condition of this instrument. With the spring ergographic curve, the sensori-motor reflex arc, after a short time, picks out such a level which shall exactly correspond to a condition of tissue equilibrium or of its working capacity, without detriment to the tissues involved. It might then be used as a means of ascertaining the working capacity of any organ to which this instrument can be applied, and to give at the same time the degree of training which it has received or is capable of receiving from time to time and under a given number of different circumstances and conditions.

The curve, therefore, must be looked upon as of the highest importance in our work. Since we know that prolonged muscular- as well as brain-work is followed by practically the same results, and that the fatigue and the exhaustion in both are due practically to the same causes, the principle and the accurate appreciation of the same underlie all educational efforts, mental as well as physical. We have the best of reasons for assuming that the activity of any organ, whether brain or muscle, when kept within its normal range of physiological endurance, excites or stimulates the growth and development of that organ by stimulating alike both the dissimilative and the assimilative phases; when carried beyond the normal range, or even the point of fatigue, it has the contrary effect.

Growth means that the supply of energy which follows a demand upon it must be greater than that amount which was demanded, for it is in this manner alone that exercise can be

followed by an increase in working capacity. The same physiological process then underlies all successful training. All training and education have their physical basis in a living organism, although every organ in it has evolved, within its own substance, its own peculiar specific energies, and the same stimulus produces reactions that differ with the particular organ upon which it acts.

But the reflex arc, through which we are trying to develop, train, and educate different parts of our anatomy, consists in all essentially of the same elementary parts, namely: (1) A peripheral sense-organ (in which we would include the tactile-, pain-, and temperature-sense in the skin); (2) an afferent nerve; (3) a sensory centre in the spinal chord; (4) an association of centres in the brain, producing conscious impressions; (5) a motor centre in the spinal chord; (6) an efferent nerve; and (7) a neuro-muscular end-organ. All these various structures are capable of being developed and trained; brought to a higher degree of efficiency, when acted upon under favorable conditions, and well within the normal physiological range of their capacity; they are liable to become fatigued and exhausted under the contrary conditions; they may also undergo repair and restitution by rest and sleep, owing to the auto-reconstructive tendencies peculiar to all living things. — For the physiologist, then, it makes no essential difference whether you train a child in the mastery of the three R's, or whether you teach it to play a musical instrument, to run or to jump, the process in its essential and elementary parts is physiologically the same in all. And, as long as the training requires the man to be in the state of consciousness, the brain, this great central power-house of his entire machinery, must always receive the attention in keeping with its importance. — Thus, training in which muscular contractions form a prominent part, in the physiological sense, is no more exclusively physical than the training of a child in the art of writing or reading is exclusively mental. In all a certain reflex sensori-motor arc, with the brain as the centre of consciousness, is engaged in doing a certain amount of work, intended for the increase of its

working capacity, and the special education of a certain part of our anatomy would simply mean that our purpose was to raise the specific energy in that particular part to a higher degree of efficiency than it could be expected to reach without such education. — Physical training has entered the scientific stage in its development, and has long since ceased to look upon the mere increase in size and strength of muscle as the highest of its aims. In training for grace and manual dexterity, for instance, the mere increase in the size of muscle may even be looked upon as a most undesirable by-product. An enlargement of the tongue would certainly not constitute the highest nor the most desirable attribute of an orator. In a most general sense, our aims are to bring about a proper and symmetrical adjustment between all the parts of our anatomy, so that, in the words of Huxley, the body becomes the ready servant of the will, and “does with ease and pleasure all the work that, as a mechanism, it is capable of,” and together with the intellect forms “a clear, cold logic engine with all its parts of equal strength and in smooth working order.”

Having dwelled briefly on the physiology of the training of the body as a whole, which practically implies an attempt of making one part of the body as good as every other part, we must now look for a moment at the physiology involved in some of the results that have been obtained by the training of special parts of our anatomy, and the relation and indirect influence which such parts bear to the rest of the body. In connection with this subject we are, in the first place, reminded of the work of Scripture, published about a year ago, on what he called “Cross-education.” The physiological principle which is involved in the results obtained by Scripture’s simple experiments seems to me of an importance so far-reaching and fundamental from the point of view of training, that it should have been followed up with greater interest. Scripture’s results would show that the exercise of one arm is followed by an increase in the strength and circumference not only of the arm thus exercised, but also of the one on the opposite side, and not doing any exercise. The measurements on that occasion were made by Dr.

Seaver, and we, therefore, must conclude that they were taken with sufficient care to insure us their accuracy and correctness.

Here, then, we would have an instance in which the special training of one part of our anatomy is seen to have an indirect influence upon remote parts. Such results as these would appear to support the idea that the exercise of our muscles might, indirectly, favor the performance of intellectual work. That this necessarily must have its normal limits we can assume with perfect certainty; but what these limits are we as yet have made little progress towards finding out. All we do know so far is that there exists a functional or physiological correlation between the different parts, as well as an anatomical one, and that, in training special parts, an overflow, as it were, occurs that affects parts remote from the one under special training.

Considerable interest has been devoted within the last two years to the subject of the relation existing between physique and mental ability. The observations of Porter, Hastings, Christopher, and myself would point to the fact that there is an undoubtedly direct relationship between the two. In a paper which has not yet been published, from the measurements of some three thousand children in Cambridge, this direct relationship is again beautifully shown to exist.

Quite recently my attention was called to an article by W. C. Bagley, "On the Correlation of Mental and Motor Ability." Bagley, from his experiments, finds an inverse relation to exist between motor and mental ability. He, moreover, finds little direct relation to exist between mental ability as represented by reaction times, and mental ability as represented by class standing, except that excellence in either is apt to be accompanied by a deficiency in motor ability. The results of Bagley are very interesting indeed, but have only a remote bearing on the subject treating of the relation between *physique* and mental work; and I should not have mentioned them in this connection had they not misled one of my friends into thinking they were contrary to those obtained by others and myself.

In so far, for instance, as Bagley's data from "experimental sources" are concerned, we will find that the tests which he made for strength, rapidity of voluntary movement, control or steadiness of motor co-ordination, etc., are all tests, combined with certain mental processes, requiring for their execution considerable training if expected to be done well. Our conclusions, on the other hand, are merely based upon physique pure and simple, as determined by a few crude anatomical measurements in a limited number of dimensions, and its relation to the mental work done by children, as the result of the training that they received in their schools. Physique, in my opinion, cannot be made to stand for motor ability. Ability is the normal function of physique, and implies a certain amount of training which is not implied necessarily in the term "physique" as determined by measurements. We may, therefore, assume provisionally, at any rate, that there exists a direct causal relationship between physique as determined by certain measurements, and mental ability as determined ordinarily in schools; for a high percentile rank, as regards physique, is almost invariably found associated with a high grade of mental work in growing children. Knowing, moreover, that muscular exercise, when administered under the most favorable physiological conditions, is followed and accompanied by an increase in growth of the height, weight, chest circumference, and muscular strength, over and above that amount which occurs without such exercise, physical training would seem to stand upon fairly solid and scientific foundations; for we now can scarcely escape the temptation of making the further deduction from the above two propositions, that whatever gives rise to increased growth in height, weight, and chest circumference must also indirectly lead to increased brain development; and, *vice versa*, whatever impairs the normal physical growth must also indirectly impair mental growth.

It is generally held that brain work has an unfavorable influence upon the growth of the body, and one of the great claims of physical trainers is that bodily exercise is necessary in order to prevent the physique of our children from break-

ing down, while their brains are being trained and educated in the schools. Undoubtedly there must be some good and cogent reasons for this general belief, but have we anything of a more scientific nature than that for our assumption? So far at least I have been unable to find anything in literature with regard to this point.

Arguing merely from analogy, it would seem rather paradoxical to a consistent physiologist to find while muscular exercise favorably influences brain development that brain exercise or work should have an unfavorable influence upon the growth of the body.

While thinking about this subject it occurred to me that one of the means of approaching the problem with a chance of getting some light on it would be to compare the growth curve between boys who went through the high school and into college and those who did not, beginning after both left the grammar school; at the same time selecting a class of boys in whom no other essential differences as regards environment and other hygienic conditions exist—in other words, boys in whom the superior mental training which they get in the higher schools can be said to constitute the chief if not the only difference influencing their lives and growth.

An approach to such a condition may be found in the difference in the training of naval cadets on the one hand and naval apprentices on the other. Both classes of boys start about the same age; their work on board ship as well as their drills on shore are almost identical; the food which they get has about the same value in calories, the difference being that the cadets are served better than the apprentices; both get at least eight hours' sleep; the cadets do about the same amount of work with their hands as do the apprentices; in fact, we have here the rather rare opportunity of comparing conditions of life in which the superior mental training received by the cadets at the naval academy may be said to constitute the chief if not the only difference. Consequently their respective growth curves when compared to one another ought to give some very valuable information with regard to this point.

The necessary material for such curves was found, partly in the growth tables published by me in 1895, partly in the tables not yet published, and compiled from the physical examination records of a large number of naval apprentices and landsmen for training.

MEAN VALUES, DERIVED FROM 4,541 CADETS AND 3,445 MEN AND BOYS, COMPARED.

AGE.	HEIGHT (In.)		WEIGHT (Lbs.)		CHEST CIRCUM. (In.)	
	Cadets.	Men.	Cadets.	Men.	Cadets.	Men.
15.	64.29	63.37	108.50	109.00	29.95	30.07
16.	65.80	64.01	116.90	114.42	31.10	30.40
17.	67.00	64.87	124.80	122.60	31.89	31.34
18.	67.63	65.43	131.80	124.94	32.68	31.80
19.	67.65	65.68	137.00	128.45	33.25	32.00
20.	68.25	65.84	138.50	133.90	33.58	32.50
21.	68.21	66.10	138.90	134.90	33.65	33.14
22.	68.35	66.31	138.70	140.08	33.77	33.62
23.	68.52	66.45	138.30	140.85	33.87	34.00

The adjoining table is intended to exhibit the differences in the mean height, weight, and chest circumference between the two classes of boys. On examining the several columns of this table, we will notice, so far as weight and chest circumference are concerned, the apprentices have a slight advantage over the cadets, beginning with a slightly higher mean in both these dimensions. As regards height, on the contrary, the cadets have a more decided advantage over the boys, having the start of the boys to the extent of a little less than one inch.

From that time on, however, the cadets rapidly gain over the apprentices and forge ahead of them in all three dimensions, up to the eighteenth and nineteenth year; the cadets

continue to keep ahead in height up to the twenty-third year, which marks practically the end of growth in height, but allowing the men to pass them in both weight and chest circumference just about the same period. The difference in the mean height between cadets and men at the twenty-third year is two inches. These conditions may be seen more strikingly represented in the three charts adjoining p. 446, this journal. This looks as if brain work might influence favorably bodily development, at least under the conditions here referred to.

The average human life in the 17th century, and, counting out the devastations caused by epidemics such as the plague, etc., was from eighteen to twenty-two years. Recent statistics have shown that this average has increased to forty and forty-five years, so that we have good reasons for supposing that a normal life, under the most favorable conditions of heredity and environment, ought to last ninety instead of seventy years. Let us try to realize and locate our relation to such a life in our capacity as teachers, trainers, or educators.

We can do this best, I think, by constructing an arbitrary binomial curve, representing the beginning, the rise, decline, and end of a normal life of ninety years' duration (see fig. 1).

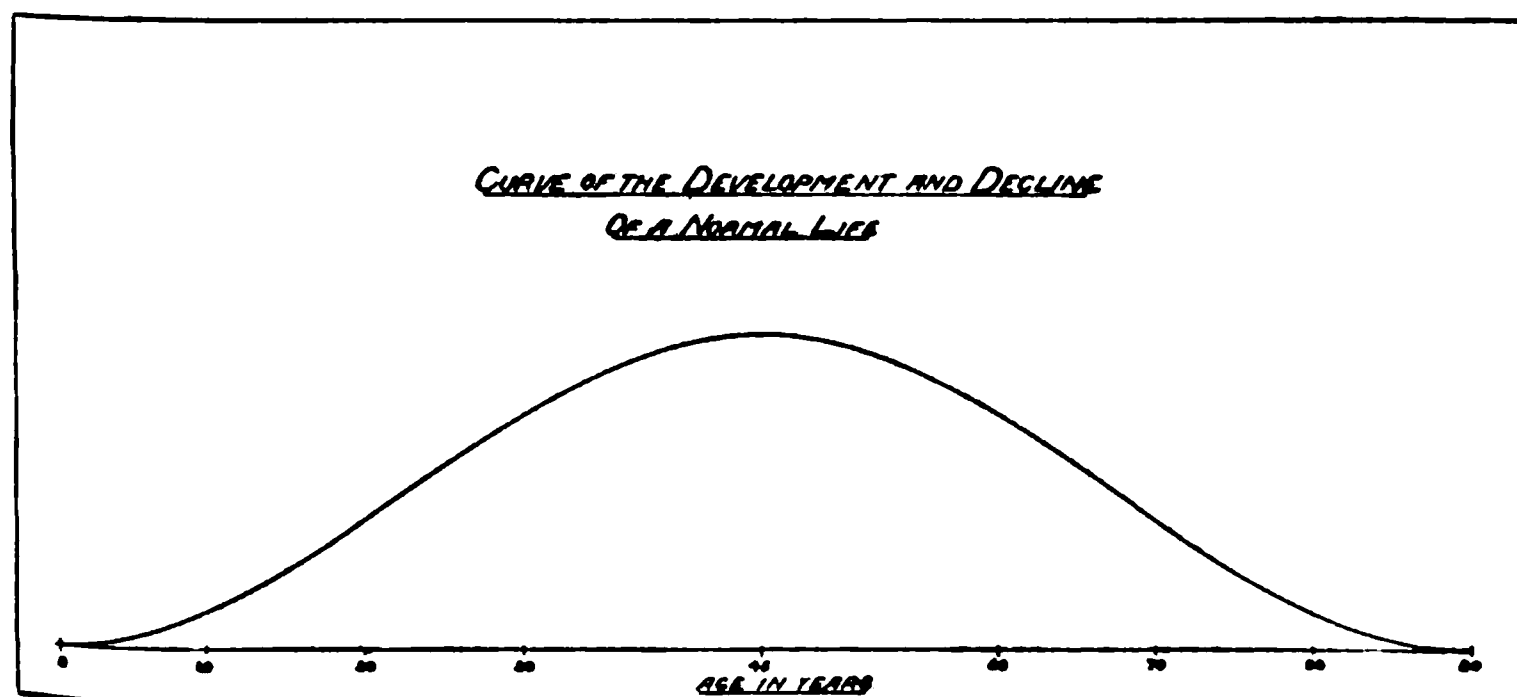


FIG. 1.

Dividing, to begin with, this curve into three great periods of thirty years each, we will note at once that the weight of our influence for either good or evil, as the case may be, falls

heavily into the middle of the first of these three periods, namely, that included between the tenth and twentieth years of life, tapering off at either end into early childhood on the one hand, and early manhood on the other. The second period, that which is included between thirty and sixty, or the middle period of life, as it might be called, is the one during which man performs his best work. It is the auto-creative period of life. The amount and quality of his work will greatly depend on how he was reared, taught, and educated, and in the free competition of life it will largely determine the rank and station which a man will attain among his fellow men, amounting in fact to an examination into his real and all around worth and value of thirty years' duration, and of an intensely practical character. While, during the third period of life, that included between sixty and ninety, a man must reap what he has sown, as it were, during both the previous periods. Here nature is very apt to prove to man, in the form of a final reckoning, that a painless decline of his years and a normal death from old age can only be the reward of a correct and useful life.

Having now localized our relation as educators to a single life, we have still much to learn by looking at the mortality curve of a whole nation. It will remind us more especially of the scope of our tasks still before us; of work yet undone or wrongly done. According to Carl Pearson, 605 out of every 1000 of children conceived, die before they are born; very many die in childhood; fewer in youth, more again in middle age, and many more still in old age. The mortality in infancy is indeed so great, that even a small reduction in the number of deaths of infants would be a readier means of checking the decline in population of some countries than would any other plan for fostering a higher birth rate.

From a statistical study of the mortality rate, Carl Pearson has made five ages of man, viz.: Infancy, childhood, youth, maturity, and senility. He has expressed his conceptions graphically in an extremely thoughtful and interesting manner. His picture shows the causeway of life in the form of a bridge on which each age is represented as passing, with

the marksman Death, hovering about and armed with different weapons of precision, killing as the men pass. The idea of the large number of ante-natal deaths is represented by man killing his own offspring with his own bones; next, during infancy, a maxim gun sweeps down the living; then, in youth, a bow and arrow is seen in the hands of the marksman; then an old blunderbuss comes; at last, a modern rifle is necessary to pick out each man because the ranks have become so thin.

Enough has been said, I think, of the value of anthropometrical records as well as statistics in general and their bearing upon the physiology of education. It was, moreover, clearly pointed out that all efforts at education, whether general or special, involve the training by exercise of a portion of the anatomy of the person to be educated; that such exercise, to have the educational value it is intended to have, must be kept well within the limits of the normal physiological range of the endurance and capacity of the parts involved. For purposes of orientation and for the study of the effects and defects of our work, of the flaws in our methods and products, and the problems to be solved in the future, we will find there is much to be learned by a consultation of our mortality statistics.

SPECIAL NOTICE.

The Journal will be published *immediately* after the meetings of the Society, and will contain authors' abstracts of the papers presented, when these papers are not given in full.

By general consent of the Heads of Departments it will contain full abstracts of experimental work carried on in the following institutions: the Medical School of Harvard University, the Experiment Laboratories of the Massachusetts General and the Boston City Hospitals, the Physiological and Biological Departments of the Massachusetts Institute of Technology, and the Anatomical Laboratory of Brown University.

Papers and abstracts of papers upon subjects connected with the Medical Sciences will be welcomed from persons not members of the Society, and if approved by the Council will be presented at the meetings, and will be given a place in the Journal.

When desired, the insertion of papers, if in abstract, will be accompanied by a note indicating the place where they may be found in full. Fifty reprints will be furnished free to authors if the desire for them be expressed on the manuscript.

Subscribers to the Journal are invited to attend the meetings of the Society.

All communications should be addressed to the Editor,

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ABERRANT PANCREAS IN THE REGION OF THE UMBILICUS.

JAMES H. WRIGHT, M.D.

(From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.)

The patient in whom this very rare, if not unique, congenital anomaly occurred was a female child of 12 years of age, who had had a little umbilical fistula since birth. This had been closed once or twice by operation, but had broken out again. It had never given any discomfort beyond its existence and the attendant moisture.

With the idea of effecting a radical cure of the condition, an operation was performed by Dr. A. T. Cabot, to whom I am indebted for the clinical facts here given. The fistulous tract was dissected out in one piece, with a good margin, down to the level of the peritoneum. The peritoneal cavity was opened and explored with the finger, but no connection of the fistula with the intestine could be made out.

The operation was entirely successful.

The fistulous tract thus dissected out in one piece was hardened entire and sections cut from different places in it to determine if possible the cause of the fistula.

Microscopical examination of these sections showed that the specimen for the most part consisted of dense connective tissue together with some fat tissue. The fistulous tract appeared to correspond to an invagination of the epidermis. In the midst of the substance of the specimen, at a point

about 2 mm. from the apex of the invagination of the epidermis, an irregularly spherical nodule was found, measuring, in the hardened section, about $3\frac{1}{2}$ mm. in greatest diameter. The general appearances of the nodule and its relation to the epidermis in the section are indicated in Plate XL., Fig. 2.

Microscopical examination of this nodule showed that it had the same microscopical structure as the pancreas. (See Plate XL., Fig. 1.) It consisted for the most part of tubules and connective tissue stroma. The tubules, in their appearance and arrangement, were like those of the pancreas; and the cells composing them were like the cells of the pancreatic tubules in morphology and staining reaction. Moreover, among the tubules undoubted islands of Langerhans were present, and also a few typical ducts lined with columnar epithelium and identical with those of the pancreas. The nodule as a whole was invested with a layer of dense connective tissue, somewhat less than 1 mm. in thickness. No efferent duct was found leading to the epidermis, although sought for in a number of sections. On account of the loss of portions of the specimen in the process of cutting the sections, it was impossible to determine whether such a duct existed or not. It seems reasonable, however, to suppose that the moisture of the parts about the fistula was due to pancreatic secretion discharged by such a duct.

The occurrence of pancreatic tissue in the region of the umbilicus can be explained as an instance of persistent omphalo-mesenteric remains. The pancreas is known to develop very early in foetal life in a region near that which afterwards becomes the umbilicus.

DESCRIPTION OF PLATE XL.

Fig. 1. Portion of section through the aberrant pancreas, showing appearances and arrangement of the tubules and two islands of Langerhans. The deep staining of the epithelial cells of the tubules is indicated. Medium magnifying power.

Fig. 2. Shows the aberrant pancreas and the relations to the invaginated epidermis. Very low magnifying power.

FIG. 1.

FIG. 2.

WRIGHT.

ABERRANT PANCREAS.

PSEUDO-PNEUMOCOCCI IN LOBAR PNEUMONIA.

OSCAR RICHARDSON, M.D.

(From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.)

The occurrence in pathological processes of capsule-bearing micrococci resembling the pneumococcus has been but rarely observed.

The first published observation of such a micro-organism seems to be that of R. T. Atkinson¹ from this laboratory, which was reported before this society in March, 1897. Other observations of similar micro-organisms are those of R. Binaghi² and of W. T. Howard, Jr.³ The micro-organisms reported by these three observers seem to be closely related to one another if not identical.

In view of the great importance of the identification of the pneumococcus, it seems to be of interest to record some additional observations of the occurrence of capsule-bearing micrococci in pathological processes, so that such micro-organisms may be more certainly differentiated from the pneumococcus.

During the past five years in the laboratory of the Massachusetts General Hospital we have found such micro-organisms at autopsy in four cases of lobar pneumonia. They were clinically and anatomically cases of acute lobar pneumonia. In none of them did death occur early in the course of the disease, and anatomically they were all in the gray stage of hepatization.

The histological examination made in three of the cases showed that the exudate was pneumonic in character, and in sections made from the consolidated lung tissue in the same cases micrococci were found in but two of the cases, and only in small number. The autopsy in the fourth

¹ Journal of the Boston Society of the Medical Sciences, Vol. I., No. 9, March, 1897.

² Ueber einen Streptococcus Capsulatus. Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten, I. Abteilung, Bd. 22, S. 273.

³ A paper read before the American Association of Pathologists and Bacteriologists, at Boston, April 6, 1901. Journal of Medical Research, July, 1901.

case was done so many hours after death that the tissues were unsuitable for histological examination. The examination of a cover-glass preparation from the affected lung in this case failed to show any micrococci, so that they must have been very few in number.

On the blood-serum cultures from these cases the micrococcus developed in small numbers from three of them, while in the fourth case the number of colonies that developed was fairly large.

A study of the autopsy records in these four cases convinces us that the same micro-organism was present in all of them, although in the cultures from one of the cases the chain formation was much more pronounced than in the cultures from the others.

The description of the micrococcus, to be given further on, is based in the finer details of cultural peculiarities upon the study of the most recent one of the cases.

We do not think that these cases are primarily due to infection with the micro-organism which we describe, because of the strong evidence in favor of the view that genuine cases of lobar pneumonia are always due to the pneumococcus, which is present in the exudate in large numbers during the height of the disease, and which rapidly disappears thereafter. We are strongly inclined to believe that this micro-organism is a secondary invader, because we have found it in the later stages of the disease, and only in small numbers in the consolidated lung tissue.

Morphology. — The micro-organism occurs in round, ovoid, or short bacillus-like forms. It is commonly arranged in pairs and sometimes in chains containing as many as 12 pairs. The individual members of a pair are often of unequal size and shape. In general it very much resembles the pneumococcus.

The thickness of the micro-organism when grown on blood serum is about half a micron. When compared with a pneumococcus grown on blood serum, the pseudo-pneumococcus is slightly larger. (Plate XLI., Figs. 4 and 5.)

On cover glasses from blood serum cultures chains are

sometimes seen in which small diplococcus forms are linked with elongated bacillus-like forms in the make-up of the chain, and in cover glasses from bouillon cultures the chains resemble short chains of streptococci.

In the tissues the micro-organism is somewhat smaller than in cultures. (Plate XLII., Figs. 6 and 7.)

In the tissues and in all the cultures the micro-organism is enveloped by a mucous-like material or capsule which takes the stain and gives the micro-organism a stained halo. In the persistence of the capsules in cultures the micro-organism differs from the pneumococcus. (Plate XLI., Figs. 4 and 5.)

The micro-organism stains with Gram's method and with the usual anilin dyes. It stains best with carbol fuchsin. It is not motile.

Cultural Characteristics.

The micro-organism grows either in the presence or absence of oxygen.

It grows somewhat better and maintains its characteristics longer in anaërobic cultures by Wright's method,¹ and in the depths of stab-cultures than in aërobic cultures.

The best growth is obtained in media of a reaction between $+0.5$ and $+1$ of the scale of the Bacteriological Committee of the American Public Health Association. In glucose agar stab-cultures, when the reaction of the medium is adjusted to between $+0.5$ and $+1$, the micro-organism exhibits its most vigorous growth, but if the reaction is brought up to $+2$, no growth is obtained.

Growth is rapid in the incubator at 37° C., and at the room temperature growth is slow.

The micro-organism dies out rather quickly in cultures, although in glucose gelatin and glucose agar cultures it may persist for several weeks.

Blood Serum. — (Löffler's mixture coagulated at 100° C.) After 24 hours in the incubator at 37° C., the colonies appear as glazed, flat, viscid, colorless, mucous-like, homo-

¹ A Simple Method of Cultivating Anaërobic Bacteria. J. H. Wright, Journal of the Boston Society of Medical Sciences, Vol. V., No. 4, Dec. 4, 1900.

geneous, irregularly outlined flecks and small patches, which may have a diameter of several mm. They may become confluent and form large areas of the mucous-like material. The water of condensation is slightly cloudy. (Plate XLI., Fig. 2.)

Glucose Agar Stab. — (Reaction $+0.5$ to $+1$.) After 24 hours in the incubator at 37° C., the growth appears as a grayish, semi-translucent band along the needle track. This band of growth in the aërobic cultures in the middle and deeper portions of the medium broadens out in one plane in ovoid shape in places to three or four times the width of the band between these extensions of the growth. The surface of the top of the medium shows a slight mucous-like patch of growth extending from the needle opening. (Plate XLI., Fig. 3.) There is no gas production.

In anaërobic cultures, the ovoid extensions of the growth are in the upper portion of the medium as well. The growth in this region is apparently favored by the absence of oxygen.

In an anaërobic glucose agar suspension culture (reaction $+0.5$), the colonies developed throughout the medium as small gray lenticular shaped discs, the largest about 3 mm. in longest diameter.

Glucose Agar Slant. — (Reaction $+0.5$.) Moderate number of colonies similar to those on blood serum.

Plain Agar Stab. — (Reaction $+0.5$.) Similar growth to that in glucose agar stab.

Plain Agar Slant. — (Reaction $+0.5$.) Similar but slighter growth to that on glucose agar slant.

Plain Bouillon and Glucose Bouillon. — (Reaction $+0.5$ to $+1$.) The growth in bouillon is slight. After 24 hours in the incubator, a slight cloudiness appears with a small amount of rather stringy looking sediment in the bottom of the tube.

In one instance where we used 100 cc. of glucose bouillon, reaction $+0.5$, the culture showed considerable clouding of the medium and a moderate amount of stringy sediment in the bottom of the flask.

FIG. 1.

FIG. 2.

FIG. 3.



FIG. 4.



FIG. 5.

RICHARDSON.

PSEUDO-PNEUMOCOCCUS.

Glucose Gelatin Stab. — (Reaction $+ 0.5$.) After several days at the temperature of the room, the growth appears along the needle track as a slender column of fine, ovoid, pearly-looking colonies. Near the top of the medium the growth fades out and is barely visible to the eye near the needle opening. There is no liquefaction of the medium.

Glucose Gelatin Slant. — (Reaction $+ 0.5$.) After several days at the temperature of the room, many colonies appear on the surface of the medium. They are fine, colorless, glazed, mucous-like, roughly ovoid in shape, and gradually form confluent streaks and patches. The colonies are pearly in appearance by transmitted light. There is no liquefaction of the medium.

Potato. — Growth is doubtful.

Milk. — After 24 hours in the incubator, the color of the medium shows a pinkish change. There is no coagulation.

Chest Fluid Agar. — After 24 hours in the incubator, the growth is similar to that on blood serum. The colonies are more pearly in appearance.

Pathogenesis.

Two brown mice and one white mouse were inoculated subcutaneously at the root of the tail, and the animals died in the course of two to three days.

At autopsy there was a widely extending œdema at the seat of inoculation and enlargement of the spleen.

Bacteriological examination of the œdema at the site of inoculation and of the liver, spleen, and blood of the heart showed the presence of the micro-organism in large numbers.

A guinea-pig, inoculated subcutaneously, died in nine days with an extensive hæmorrhagic fibrinous exudation in the subcutaneous tissues and enlargement of the spleen. A second guinea-pig, inoculated in the peritoneal cavity, died in two days with a sero-fibrinous exudate in the peritoneal cavity and enlargement of the spleen.

Bacteriological examination of both of these animals showed large numbers of the micro-organism in the exudates and in the liver, spleen, and the heart blood.

The micro-organism isolated from two of the other cases, referred to in the first part of this paper, was found to be pathogenic to guinea-pigs.

Two rabbits inoculated in the ear vein survived the inoculation with no remarkable symptoms.

Toxine Production.

Experiments made to determine the presence of a toxic substance in bouillon cultures gave no positive results.

The animals (one mouse and several guinea-pigs) were inoculated with a bacteria-free filtrate of different ages from plain bouillon and sugar bouillon cultures and with a plain bouillon culture heated to 68° C. for one hour. The quantity of the fluid injected into the animals varied in amount up to 3 or 4 cc.

Summary.

The chief points of difference between this micro-organism and the pneumococcus summed up briefly are as follows:

The capsules of the pseudo-pneumococcus persist in cultures, while those of the pneumococcus do not.

On the surface of coagulated blood serum the colonies of the pseudo-pneumococcus are many times larger than those of the pneumococcus under the same conditions and are entirely different in character. They may become confluent and form a mucous-like scum, which the colonies of the pneumococcus never do. (Plate XLI., Figs. 1 and 2.)

In glucose agar stab-cultures the growth of the pseudo-pneumococcus is quite unlike that of the pneumococcus, and on gelatine at the room temperature its comparatively luxuriant growth is in marked contrast with the scanty growth of the pneumococcus.

These points of difference appear to be sufficiently marked to justify the opinion that this micro-organism has an identity separate from that of the pneumococcus and that it should be distinguished from it.

FIG. 7.

RICHARDSON.

PSEUDO-PNEUMOCOCCUS.

DESCRIPTION OF PLATES XLI. AND XLII.

PLATE XLI.

Fig. 1. Pneumococcus. Twenty-four-hour old aërobic blood-serum culture.

Fig. 2. Pseudo-pneumococcus. Twenty-four-hour old aërobic blood-serum culture.

Fig. 3. Pseudo-pneumococcus. Twenty-four-hour old glucose agar stab-culture.

Fig. 4. Pseudo-pneumococcus. Cover-glass preparation from blood-serum culture stained with carbol fuchsin. X 2000.

Fig. 5. Pneumococcus. Cover-glass preparation from blood-serum culture stained with carbol-fuchsin. X 2000.

PLATE XLII.

Fig. 6. Pseudo-pneumococci in a cover-glass preparation from the liver of a mouse. Stained with carbol fuchsin. X 1500.

Fig. 7. Pseudo-pneumococci in a section of a pneumonic lung stained by Gram's method and with eosin, after hardening in Zenker's fluid. The section two micra thick, cut in paraffin on the Minot-Blake microtome. X 1500.

A PSEUDO-TETANUS BACILLUS.

JOHN B. BAIN.

(From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.)

This organism was obtained from a blank-cartridge wound of the lower third of the thigh.

The patient was a boy, who came to the Out-Patient Department of the Massachusetts General Hospital in the service of Dr. Farrar Cobb on July 2, 1900. The wound had been received about one week before coming to the hospital. It extended about $2\frac{1}{2}$ inches into the extensor muscles of the thigh.

On account of the frequency with which tetanus follows blank-cartridge wounds the tissues about the wound were excised by Dr. Cobb as a prophylactic measure, and the material thus removed was sent to the laboratory to be examined for tetanus bacilli.

From this material a blood-serum tube was inoculated, and in this tube, after some days, there was found to have developed numerous slender bacilli, many of which bore round spores at one end. Numerous micrococci had also developed. At this time these bacilli were regarded as tetanus bacilli, on account of their having round end-standing spores so characteristic of the tetanus bacillus, and on account of the source of the material from which they came.

The patient made an uninterrupted recovery from the operation and never showed any symptoms of tetanus.

The tetanus-like bacillus was isolated in pure culture and was found not to be the tetanus bacillus, although having much resemblance to that organism and being, like it, an obligate anaërobe.

Inasmuch as the number of known species of obligate anaërobes is small, and inasmuch as this organism may be readily mistaken for the tetanus bacilli, it has seemed desirable to put on record a description of this pseudo-tetanus bacillus.

The description follows:

Morphology. — (Plate XLIII., Figs. 1, 2; Plate XLIV., Fig. 5.) A bacillus with rounded ends, variable in length and about 0.5 micron thick. It may appear as long filaments more or less segmented. It stains homogeneously with the ordinary dyes in young cultures, but in old cultures rods with oblong unstained areas in their substance may be seen. It decolorizes by Gram's method. It is not motile, but has fairly numerous delicate flagella, which have been demonstrated with the aid of an unpublished method devised by Dr. Hugh Williams. (Plate XLIV., Fig. 5.) It has no capsule.

The bacillus produces spherical spores situated at the end of the rod. (Plate XLIII., Figs. 1 and 2.) They are most abundantly developed in blood-serum cultures. In its spore formation and in its dimensions the bacillus closely resembles the tetanus bacillus. A slight club-shaped swelling at one end of the rod is occasionally seen. This is regarded as due to involution or as abortive spore-formation, for it is seen especially in cultures in which spore-formation is not active. The spores survive heating at 80° C. for 30 minutes and at 100° C. for 5 minutes.

The bacillus is an obligate anaërobe. It grows well in the incubator at 37° C., but very slowly and feebly at the temperature of the room.

Colonies in One Per Cent. Glucose Agar. — (See Plate XLIII., Fig. 3.) Discrete colonies of the bacillus were obtained in glucose agar in "suspension cultures" and in Petri plates by means of a modification of the mica plate method. These Petri plate cultures were made by pouring a quantity of fluid and infected agar into the upturned cover-dish of the pair, then placing in this the other dish, bottom down, and allowing the agar to harden between the two glass surfaces. The colonies developed in the layer of agar thus formed and chiefly in the central portions of the plates.

The colonies in glucose agar in 24 to 48 hours appear as minute grayish points with hazy outlines. Older colonies may attain a diameter of 2 or 3 mm. and appear as grayish, hazy masses with whitish, opaque centres. The margins of

the colonies are distinctly fuzzy. Under the microscope the colonies are seen to be made up of interlacing filaments, which extend into the surrounding medium sometimes in a more or less radiate manner. (See Plate XLIII., Fig. 3.) At the centre of a colony the filaments may be so closely matted together as to make this region opaque and granular in appearance.

As compared with the colonies of the tetanus bacillus, the colonies of this bacillus develop more slowly, are not so fuzzy, and under a low magnifying power of the microscope the filaments at the periphery do not extend so far away from the body of the colony, while at the central portion of the colony the filaments are more closely packed together.

Stab-Cultures in One Per Cent. Glucose Agar. — (Reaction + 1 of the scale of the Bacteriological Committee of the American Public Health Association.) After 24 hours a white streak is generally seen along the line of inoculation. This extends to a point several millimetres from the surface of the medium. If left in the thermostat for several days, this grayish streak gradually enlarges in width and sends out short lateral outgrowths into the medium, thus producing a fuzzy appearance along the line of inoculation. The general appearance of the fully developed growth has been likened to a test-tube brush. (Plate XLIII., Fig. 4.) The growth somewhat resembles that of the tetanus bacillus, but the lateral outgrowths do not extend as far out into the medium as in the case of that bacillus. (Plate XLIV., Fig. 6.) No gas bubbles are produced in the medium. There is no development of odor.

Löffler's Blood Serum, Coagulated at 100° C. — (Anaërobic tube cultures according to Wright's method.¹) After 48 hours in the incubator, the growth appears on the surface as grayish, viscid colonies a fraction of a millimetre in diameter. They later may become confluent and form a scum. The blood serum is slowly liquefied and a quantity of gas is formed. A peculiar foul odor is developed.

¹ A Simple Method of Cultivating Anaërobic Bacteria, by J. H. Wright. Journal of the Boston Society of Medical Sciences, Vol. V., No. 4, Dec. 4, 1900.

Bouillon. — (Tube cultures under anaërobic conditions according to Wright's method.) Diffuse clouding of the medium after 48 hours in the incubator with the eventual deposit of an abundant viscid, stringy, whitish sediment. No surface pedicle is formed. The growth is more vigorous in bouillon containing 1 per cent. glucose. No marked change is produced in the reaction of plain bouillon by the growth of the bacillus in it. In the fermentation tube only a small amount of gas is produced from glucose bouillon.

One Per Cent. Glucose Gelatine Stab-Cultures. — In the course of 2 or 3 weeks a few spherical, whitish colonies a fraction of a millimetre in diameter develop in the depths of the medium. The gelatine is not liquefied.

Litmus Milk. — (Under anaërobic conditions by Wright's method.) There is no growth of the organism in this media.

Potato. — (Anaërobic cultures by Wright's method.) No growth.

Dunham's Pepton Solution. — No growth.

Reaction of Culture Media. — In general a degree of acidity to phenolphthalein of $+0.5$ to $+1.0$ of the scale of the Bacteriological Committee of the American Public Health Association seems to be more favorable for the rapid, vigorous growth of this bacillus than a reaction $+1.5$.

Pathogenesis. — The inoculation of guinea-pigs gave no result.

This bacillus shows the following chief points of difference from the tetanus bacillus:

It decolorizes by Gram's method, while the tetanus bacillus does not. Its flagella are not as numerous as those of the tetanus bacillus. It is not pathogenic for guinea-pigs, while the tetanus bacillus is markedly pathogenic for these animals. Among other cultural differences, its growth in glucose gelatine and glucose agar stab-culture is totally unlike that of the tetanus bacillus in these media. It does not liquefy the gelatine, while the tetanus bacillus does.

DESCRIPTION OF PLATES XLIII. AND XLIV.

PLATE XLIII.

Fig. 1. Cover-glass preparation of pseudo-tetanus bacilli, showing spores. Several degenerate, irregularly staining rods are also shown. X 2000.

Fig. 2. Shows spores in process of development. X 2000.

Fig. 3. Colony of the pseudo-tetanus bacillus in glucose agar.

Fig. 4. Stab-culture of the pseudo-tetanus bacillus in glucose agar.

PLATE XLIV.

Fig. 5. Pseudo-tetanus bacilli with flagella stained by the method of Dr. Hugh Williams.

Fig. 6. The tube on the extreme right is a suspension culture of the pseudo-tetanus bacillus in glucose agar. The tube next to this is a stab-culture of the pseudo-tetanus bacillus in glucose agar. The two tubes on the left are stab-cultures of the tetanus bacillus in glucose agar, showing the wide pervasion of the medium by the growth of the tetanus bacillus, producing a hazy appearance extending far into the medium from the line of inoculation. The difference in appearance between the growth of the true tetanus bacillus and that of the pseudo-tetanus bacillus in glucose-agar stab-cultures is shown.

FIG. 1.

FIG. 2.

FIG. 3.

BAIN.

FIG. 4.

PSEUDO-TETANUS.

FIG. 6.

BAIN.

PSEUDO-TETANUS.

SEASONAL VARIATIONS IN GROWTH OF BOYS BETWEEN THE AGES OF SEVEN AND FOURTEEN YEARS.

F. W. HITCHINGS AND G. W. FITZ, M.D.

The examinations were made at the Boys' Home in Dedham, a branch of the Boston Children's Friend Society. All the children were weighed stripped, once a week, and heights were measured every three months, except on the third quarter, which occurred in August. Twenty out of the thirty boys in the home remained throughout the year, and these only are considered. The results of the study are as follows:

(1.) Variations in weight amounting in some cases to as much as five pounds were observed in most of the boys from week to week. These variations were so numerous and so marked as to suggest that any single test of an individual is liable to a plus or minus error of several pounds, and that successive weighings are necessary for accuracy.

(2.) Over 90 per cent. of the total increase in weight occurred during the period from June to December. This is in essential accord with Malling-Hansen's results.

(3.) During the period from January to June the weight fluctuated without definite gain or loss, constituting a period of minimum growth. This seems to be made up of shorter periods of gain and loss which practically neutralize each other and are more or less variable in their occurrence and in their range in different individuals.

(4.) The weight fluctuations are much more marked during the period of minimum growth in weight than during the period of maximum growth. This seems to indicate that there is less resistance to external influences during this time, and that on the whole the vitality of the child is at a lower level.

(5.) A preliminary study of the weather conditions in connection with these curves of growth shows that rainfall, temperature, and barometric pressure had slight, if any, influence. Humidity, on the other hand, seems to have had some

influence during the period of minimum growth. Malling-Hansen reported that temperature controlled growth in some degree.

(6.) The general form of the curve of growth in weight was found common to all the individuals studied (20), covering the ages seven to fourteen. The larger minor fluctuations were also found to be common to the majority of the boys, suggesting that the causes were general rather than individual, and that growth throughout this age period has the same general seasonal variation.

(7.) Growth in height in the majority of cases showed either a continuous increase at the same rate throughout the year or more rapid growth during the period of most rapid growth in weight. Three boys only showed correspondence with Malling-Hansen's conclusions, that is, more rapid growth in height during the resting period of growth in weight.

STUDIES UPON BACTERIOLYSIS AND TYPHOID IMMUNITY.

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*(From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.)**(Abstract.)*

In this series of observations the writer has studied the effect upon typhoid bacilli of typhoid blood serum alone and in combination with normal serum. The addition of normal serum was suggested by the success of Bordet and Ehrlich in producing the so-called "hæmolytic" sera.

In the solution of red corpuscles by the hæmolytic serum it was found that two different elements were necessary: first, a specific immune element, and secondly, a non-specific normal element or ferment. The immune element acted as an intermediate body binding the ferment to the special cell, which was then destroyed. Similar laws were found to govern the bacteriolytic phenomena which were produced when typhoid and cholera sera were brought in contact with their respective bacilli.

In this study the blood serum of forty-one typhoid patients was investigated at various stages of the disease and convalescence to determine in the first place whether such serum was ever markedly antagonistic to the growth of the typhoid organisms, and, if not, whether the addition of normal serum would increase its power.

Conclusions.

I. In typhoid fever nature produces a cure through bactericidal agents acting upon the specific bacilli. These agents are produced by the body cells, especially those of the lymphatic apparatus, and are found in varying amounts in the blood.

II. These protective agents are at least two in number — a specific immune element, and a non-specific element or ferment.

III. It is the function of the immune element to bind the complement or ferment to the bacterial cell, which is then destroyed.

IV. In the earlier and middle stages of the disease the immune body may apparently be present in large amount and yet be of little value, because of the absence of the complement.

V. In the stage of convalescence or falling temperature the normal element returns apparently to the blood, and a corresponding destruction of bacilli takes place. Further, inasmuch as this marked destruction of bacilli must set free an excess of typhoid toxin contained in the bacterial cells, we have in this fact a possible explanation of the marked remissions of temperature seen clinically in the fourth week of the disease.

VI. Inasmuch as the addition of normal serum to the inactive serum of the typhoid patient will, in most instances, make that serum more powerful, in fact, make it very similar to the serum found in the fourth week, we should be justified theoretically in treating such patients with normal serum.

VII. It will probably be found, however, that in certain cases the blood of the patient will lack both immune and normal elements, and that both of these will have to be supplied. Just which elements are necessary can be determined probably by submitting the patient's blood to tests similar to those described.

VIII. The blood of a normal individual may, under certain conditions, have very destructive power upon typhoid bacilli. This power is due, undoubtedly, to substances very similar to those found in typhoid serum. Their relation to the subject of natural immunity is, of course, of the greatest importance, and needs much further study.

IX. The principles set forth above may apply to infections other than typhoid. This question should be investigated.

(NOTE. To be published in full in *Journal of Medical Research*, July, 1901.)

RETROGRADE METAMORPHOSIS IN THE FAUCIAL TONSILS.

J. L. GOODALE.

The object of the following paper is to describe the histology of the retrograde changes occurring in the faucial tonsils. While a general statement of these appearances is given in most text-books of histology and laryngology, I have been unable to find any account which represents the extent of our present information. Within two or three years much has been added to our knowledge of the endothelial and epithelioid cells of the reticulum, while the significance of plasma cells has only recently been a subject for investigation. Our information regarding these cells has been derived chiefly from the study of hypertrophied and inflamed tonsils, lymph glands, and other tissues. No investigation has been made, so far as I am aware, regarding their occurrence in tonsils which have experienced retrograde changes. In such tonsils there are several other points of interest which deserve attention. These relate to the changes in the epithelium of the crypts and the alterations in the connective tissue.

In the present study a series of tonsils was investigated, some which had been removed during life, and others obtained from autopsies where it was possible to remove a considerable portion of the surrounding tissue. The advantage of this is obvious as compared with the simple excision of the tonsil during life, since in the latter case complete removal is seldom possible. The subjects from which the tonsils were obtained ranged from 50 to 65 years of age. Macroscopically the tonsils averaged 1 cm. by 2 cm. in diameter, and, except for the adhesion of the pillars in some instances, presented no abnormalities.

Immediately after excision, small portions of the tissue were placed in fixing fluids. Of these the most suitable for general purposes is Zenker's fluid, as it not only gives the best results, when followed by polychrome methylene blue

and eosin, in the study of the germ centres, but is also an excellent fixative for Mallory's triple connective tissue stain. The value of this latter in the study of the tonsil cannot be overestimated, as it demonstrates the finer fibrillæ in a manner unapproached by any other stain. Alcohol, as a fixing agent for the cellular structures, was exceedingly unsatisfactory. In all cases paraffin embedding was employed.

In all the cases examined the mucous membrane covering the free surface of the tonsil appeared unusually thick and compact, and showed almost no penetration from polynuclear neutrophiles. Except for this, its general structure did not differ from that usually encountered in childhood. The mucous membrane of the crypts varied considerably in the different specimens examined. In some instances it resembled that of the young tonsil, being loose in texture, its deficiencies crowded with lymph cells, plasma cells, and polynuclear neutrophiles. In such tonsils the follicles are comparatively normal, and show a fairly active proliferation. In other cases the mucous membrane of the crypts is more like that of the free surface of the organ in its compact structure, and shows but little migration of leucocytes. The follicles in the vicinity here are seen to be much smaller than usual, and show little or no evidence of proliferation.

The amount of lymphoid tissue, in proportion to the connective tissue, was in all cases less than that found in early life. The section stained by Mallory's method for connective tissue gives the best demonstration of the sclerotic process. The distribution of the two tissues follows in general one of two plans. Either the fibrous hyperplasia predominates in the region of certain of the chief fibrous trabeculæ, or is chiefly limited to the vicinity of the capsule at the base of the organ. In the first form, where this sclerosis occurs mainly along the larger fibrous trunks, it is most distinctly marked near the base of the tonsil, but may extend upward even to the mucous membrane of the free surface. It is usually more marked along some of the trabeculæ than along others. The connective tissue fibres extend in the sclerosed

areas from the primary trunks outward, surrounding the blood-vessels with irregular, closely-appressed bands, the fibres containing here and there lymphoid cells in the interspaces. As one passes in the direction of the crypts, these fibres are seen to be smaller and more loosely woven, but they may be traced directly from the trabeculæ to the crypts. The lining endothelium of the connective tissue is much less conspicuous than in the young tonsil, and shows little tendency to proliferate. In the regions occupied by the follicles these connective tissue fibres become extremely delicate and widely separated by masses of lymphoid cells, but may, however, be traced into the centre of the follicles. In these areas of sclerosis the follicles are seen to have undergone various degrees of retrograde metamorphosis, as will be later described. Such areas may adjoin on either side areas in which large active follicles occur, essentially similar to those of the young tonsil. It was noted that the follicles in the immediate vicinity of the crypts were the largest and most active, while those more remote from the crypts showed a greater amount of atrophy. Many of the most markedly atrophied follicles were situated immediately below the compact epithelium of the free surface of the organ. In certain portions of the dense tissue in the interior of the tonsil, traces may be seen here and there of preëxisting follicles, as indicated by small collections of lymphoid cells, no distinct germ centre being visible.

The blood-vessels in the sclerosed areas show generally a thickened wall, lined with normal endothelial cells. Sections stained by Weigert's resorcin-fuchsin method show no apparent change in the elastic tissue of the arteries.

The other variety of sclerosis begins in the vicinity of the base of the tonsil and extends from this portion upward. The tonsil is here divided sharply into two well-defined areas: a lymphoid area occupying the region adjoining the mucous membrane of the free surface of the tonsil, and the connective tissue area, which makes up the rest of the organ in the vicinity of the base. In the most marked example of this sort, from a man 65 years of age, the site of the tonsil

was seen to be occupied for one-fourth of its area with lymphoid tissue, and the remaining three-fourths with connective tissue and fat tissue. (Plate XLV., Fig. I.) The lymphoid tissue presents a comparatively homogeneous appearance. Scattered about in it, and situated chiefly in the vicinity of the crypts, were follicles, all of extremely small size with the exception of one or two near the orifice of the crypt. The capsule at the base is composed of dense tissue traversed by thick-walled blood-vessels. This connective tissue is about 2 mm. in thickness, and separates completely the tonsil from the muscle fibres beneath. Within the capsule the connective tissue becomes of extremely loose texture, the fibres forming a large-meshed network with rounded intercellular spaces, containing fat, aggregated into irregular groups separated by dense bands. The general direction of the fibres occupying this region is parallel with the long axis of the tonsil. In the portion of the connective tissue nearest the lymphoid area it appears possible to trace the method of origin of this network. At intervals a separation is seen to occur between two parallel fibres for a short distance, with the result of producing an oval deficiency between them, which contains fat. Delicate fibrillæ may be seen crossing these spaces in an irregular fashion. These fat spaces are generally arranged in a linear manner. They become larger and more numerous as the capsule of the tonsil is approached, and are there aggregated into a large-meshed network.

In both forms of sclerosis the first indication of retrograde change in the follicles consists in a shrinkage of their endothelial reticulum. This diminishes in size from loss of the endothelial cells in proportion to the degree of atrophy present, becoming in the more advanced stages hardly recognizable, or disappearing altogether. (Plate XLV., Fig. II.) Endothelial proliferation is correspondingly less evident, and many follicles show no mitotic figures. The lymphoid cells surrounding the germ centre do not, however, diminish in number at the same rate as the endothelial cells of the reticulum. In follicles where in cross-section the endothelial reticulum has been reduced to from six to fifteen cells there usually remains

a broad, well-developed ring of lymphoid cells. In these atrophied follicles there appears to be little or no migration of lymphoid cells, although the surrounding lymph channels contain irregular lines of lymphoid cells. These lines do not, however, follow a definite direction, as is the case with those proceeding from the actively functioning follicles in the vicinity of the crypts. While the greater portion of these tonsils are in a state of inactivity, as shown by the small follicles without proliferating germ centres, a certain amount of function usually remains. This is evidenced by the fact that a few follicles were in all cases found situated near the crypts, of essentially full size, which showed proliferating endothelial cells, epithelioid cells with incorporated lymphoid cells, plasma cells, and nuclear detritus. These active follicles were always found close to a crypt, and generally near its orifice.

A certain amount of light may, perhaps, be thrown on the nature of these changes by the study of the histological phenomena occurring in an acutely inflamed, partially atrophied tonsil, which was removed during life from a woman 35 years of age. Clinically this tonsil was seen to be about 1 cm. by 2 cm. in transverse section, to be remarkably firm in consistence, covered with a smooth mucous membrane, and showing only a few small crypts. It was slightly redder than normal, and a moderate amount of swelling existed in the circumtonsillar region. There had been moderate pain in the throat, and constitutional disturbance, for several days. The condition was probably a beginning circumtonsillar abscess. After excision of the tonsil the symptoms rapidly disappeared. Histological examination showed evidence of a moderate degree of proliferative inflammation occurring in a tonsil which was the seat of irregular areas of sclerosis. These sclerotic areas are situated in two of the larger fibrous trunks and extend to the mucous membrane of the free surface. In one of the areas mentioned may be seen in cross-section from ten to twelve follicles which have undergone various degrees of retrograde metamorphosis. These join on either side areas in which large follicles are situated, which are normal except

for the proliferative inflammation. In these latter areas the phagocytic epithelioid cells in the follicles are numerous, and are seen to be actively engaged in incorporating other cells and cellular detritus. In those follicles, on the other hand, which are more or less atrophied, yet still preserve a certain amount of their germ centre, there is little or no proliferation of the endothelial cells present, and phagocytic cells are almost wholly absent. Many of these atrophied follicles are situated immediately below the compact mucous membrane of the free surface of the tonsil. It was especially noted that those follicles in the immediate vicinity of the crypts have suffered the least from atrophy and are the most active participants in the acute inflammation, while those follicles which are most remote from the epithelium of the crypts have experienced the greatest amount of atrophy, and share but little, or not at all, in the inflammatory process.

As pointed out by the writer in a former paper, the histological alterations in acute proliferative tonsillitis are probably due to the absorption of toxins from the crypts. The infecting bacteria multiply as in a culture tube, producing their toxins, which are absorbed by the tissues of the tonsil, giving rise there to endothelial proliferation. Mallory has concluded from his observations that strong toxins cause degeneration or necrosis of cells and exudation, while dilute or weak toxins produce proliferation and phagocytosis.

These views, if accepted, serve to explain why in an atrophied tonsil the follicles nearest the crypts continue more active than those which are more remote. The contents of the crypts, composed as they are of the fluids of the mouth, detritus, and bacteria, may be supposed to constitute a stimulant to endothelial cells, in a manner similar to a weak toxin. This fluid continually enters the tonsillar tissue and produces proliferation and phagocytosis in the reticulum of the organ. Those endothelial cells which are exposed to the action of this fluid would naturally continue in a state of activity longer than those which are removed from its influence. On this hypothesis the follicles nearest the crypts

would remain larger and more active than those at a distance, and as just stated, this is actually the case. Furthermore, in these senile tonsils, many follicles situated immediately below the compact epithelium of the free surface exhibit more or less advanced atrophy and, as is well known, this epithelium forms a relatively efficient barrier against the penetration of foreign substances. In this connection the writer would recall the histological appearances found in tonsils which contain cheesy accumulations in their crypts. In such tonsils proliferation and phagocytosis is extremely conspicuous. It is reasonable to suppose that the fluids absorbed from the offensive plugs constitute a stronger irritant to the endothelium of the organ than the fluids formed in smaller and better drained crypts.

The results of this investigation show that retrograde metamorphosis in the faucial tonsils begins in the regions where the connective tissue originally predominated, namely, in the trabeculæ and fibres of the capsule. It may progress either along the trabeculæ in the form of an irregularly distributed sclerotic process, or in a more homogeneous and symmetrical manner, proceeding from the base of the organ towards the mucous membrane of its free periphery. In the sclerosed areas the endothelial cells of the reticulum exhibit less evidence of proliferation and become fewer in numbers. Later those forming the germ centre of the follicle entirely disappear, and there is left to represent the follicle merely a heap of lymphoid cells, which progressively decrease in number until finally the former site of the follicle is occupied wholly by connective tissue in which fat may be deposited. The follicles most remote from the crypts experience the greatest amount of atrophy, while those nearest the crypts, and those particularly nearest the orifice of the latter, preserve correspondingly best their functional activity.

[My thanks are due to Dr. Charles S. Minot of the Harvard Medical School and to Dr. J. H. Wright of the Massachusetts General Hospital for the facilities kindly extended to me in their respective laboratories.]

DESCRIPTION OF PLATE XLV.

FIG. I. Section of tonsil, stained with hæmatoxylin and eosin, 20 mm. objective. Here the lymphoid tissue is slightly developed, and the fibrous tissue correspondingly better marked. The fat occupies the larger part of the field, but is still seen to be separated by the fibrous capsule from the surrounding muscles.

FIG. II. Section through a small atrophied follicle from preceding case. This is seen in the centre of the field as an oval area, consisting of endothelial cells, surrounded by an irregular ring of a few layers of lymphoid cells.

FIG. 1.

FIG. 2.

GOODALE.

TONSILS.

PROGRESSIVE MUSCULAR ATROPHY, WITHOUT INVOLVEMENT
OF THE PYRAMIDAL TRACTS.

E. W. TAYLOR, M.D.

(From the Sears Pathological Laboratory, Harvard Medical School.)

At the meeting of the American Neurological Association, May, 1900, in the course of a discussion on the neurone doctrine in its relation to disease of the nervous system, Spiller¹ discussed the pathological changes in the neurone, with special reference to the question of the support pathological anatomy affords to the theory of the identity of the neurone. The general conclusion reached in this analysis of cases reported in the literature and of his own is that degeneration transmitted from one set of neurones to others functionally associated is an unusual occurrence. Regarding the motor neurones, he quotes Senator's classical case of amyotrophic lateral sclerosis without visible pathological change in the pyramidal tracts, and also cases reported by Dejerine, in which progressive muscular atrophy of the spinal type had existed for eighteen and ten years respectively, with no detectable degeneration of the pyramidal tracts.

The following case is of interest in this connection as bearing out the general proposition shown in Dejerine's cases, for example. The man from whom the spinal cord² was taken had exhibited himself during the latter years of his life as a "living skeleton," at cheap museums. He died many years ago, and so far as I am aware a diagnosis of his disease was not made during his life. Details of the autopsy are also lacking, but sections from different parts of the cord were made, and stained by several methods, of which the most useful for our purpose are those stained by carmine and by Weigert's myeline sheath method.

The lumbar enlargement shows in a given cross-section not more than a dozen nerve cell bodies in the two ventral

¹ W. G. Spiller: The Pathological Changes in the Neurone in Nervous Disease. Trans. of Am. Neurolog. Assn., 1900.

² For the preparations I am indebted to Dr. W. F. Whitney.

horns, and of these the nuclei are highly indistinct or wholly lacking, and the pigmentation excessive. These few remaining cells are located at the periphery of the horns; none are to be made out in the central portions. A Weigert specimen shows an almost complete loss of myelinated fibres and collaterals in the ventral horns, and an extreme, though not absolutely complete, degeneration of the ventral nerve roots. In spite of this destruction of the primary neurones, the secondary neurones — pyramidal tracts — show no sign of degeneration. A similar condition exists in the thoracic region, and still more marked alterations of a similar character are found in the cervical enlargement. Here there is practically a complete disappearance of ventral nerve cells, with a corresponding degeneration of nerve roots. The neuroglia shows the usual overgrowth, with a considerable number of large spider cells. The horns contain a few more or less degenerated myelinated fibres. Beyond a possible very slight overgrowth of the neuroglia in the lateral columns, no change in the pyramidal tracts is to be made out. It is furthermore worthy of note that what change is observable in the neuroglia is not confined to the region of the pyramidal tracts, but involves other portions of the white matter as well. Changes in the myeline which would indicate a true neurone degeneration are not to be found anywhere in the white matter, excepting in the emerging ventral roots. (See Plate XLVI., Figs. 1 and 2.)

From these findings it is clear that the disease from which the patient suffered was progressive muscular atrophy of the spinal type. The pathological interest of it lies in the fact that the atrophy of the peripheral motor neurones may be regarded as essentially complete, while the central associated motor neurones remain wholly uninvolved. This case, therefore, bears out the general proposition made by Spiller, as a result of his investigation, that in spite of long-continued degeneration, and consequent impairment of function of one set of neurones, closely related neurone systems may remain unimpaired, at least for long periods of time. In making this statement, reliance is of course placed on the appearances

FIG. 1.

FIG. 2.

TAYLOR.

MUSCULAR ATROPHY.

as given by the Weigert method. It is not to be denied, and in fact is highly probable, that more refined methods, such as may possibly develop from Apáthy's researches, would reveal changes in the central neurones of a characteristic sort. In the meantime, however, such cases as the one above reported force us to the assumption that neurone systems are essentially independent anatomically, however close their functional association may be. In the few instances in which slight alterations have been found in secondary neurones, it is probable that such changes are due to the cessation of function (Goldscheider) rather than to an interruption of anatomical continuity.

DESCRIPTION OF PLATE XLVI.

FIG. 1. Cervical cord: Weigert stain, showing the integrity of the pyramidal tracts.

FIG. 2. Same. Ventral horn: higher power, showing disappearance of myelinated fibres in the ventral horns, and the absence of nerve cells. Degenerated ventral nerves may be seen at the lower side of the figure.

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